Effects of Bovine Prostate Powder on Zinc, Glucose, and Insulin Metabolism in Old Patients With Non–Insulin-Dependent Diabetes Mellitus

M.K. Song, M.J. Rosenthal, B.D. Naliboff, L. Phanumas, and K.W. Kang

Since rabbit prostate extract strongly stimulated intestinal zinc absorption and improved the diabetic condition of streptozotocin-induced diabetic rats, we examined the effects of 200 mg bovine prostate powder supplemented with 20 mg zinc (Pro-Z) on the clinical manifestations of older male patients with type II diabetes. Twenty-two male patients who received Pro-Z capsules two to four times per day for 3 months showed reduced mean fasting blood glucose levels from 202 to 169 mg/dL, hemoglobin A_{1C}-(HbA_{1C}) concentrations from 12.2% to 9.5%, and mean values for the 3-hour area response above the fasting glucose concentration (TAFGC) from 141 to 102 mg glucose/dL/h. In eighteen patients who received placebo, mean values for fasting blood glucose decreased from 167 to 165 mg/dL and HbA_{1C} from 10.4% to 10.2%, and for TAFGC increased from 121 to 126 mg glucose/dL/h. No detrimental changes occurred in the liver and kidney function of patients receiving either Pro-Z or placebo. However, blood cholesterol and low-density lipoprotein in patients receiving Pro-Z decreased slightly, whereas values in the placebo group tended to increase. The mean fasting plasma insulin decreased 15.5 to 13.8 μU/mL in subjects given Pro-Z, while the zinc concentration increased from 1.21 to 1.39 μg/mL. In contrast, the mean value for plasma insulin in the placebo group changed from 14.4 to 15.4 μU/mL (worsened), and for zinc, from 1.24 to 1.30 μg/ml. Interestingly, fasting urinary glucose concentrations in subjects given Pro-Z decreased from 1,249 to 378 mg/dL, whereas in those given placebo the values changed from 877 to 778 mg/dL. Since plasma zinc concentrations in both the placebo and the Pro-Z group were normal, these results suggest that biochemical constituents in the prostate including zinc may be involved in controlling glucose metabolism in patients with non–insulin-dependent diabetes mellitus.

ZINC PLAYS A KEY ROLE in the regulation of insulin production by pancreatic tissues and glucose utilization by muscle and fat cells. The abilities to synthesize and secrete insulin and to use glucose are impaired in the zinc-deficient state.[1,2] Intestinal zinc absorption rates and plasma zinc levels in diabetic patients are reduced.[3-6] Zinc is involved in the regulation of insulin receptor–initiated signal transduction mechanisms[2] and insulin receptor synthesis.[7] Thus, normalization of intestinal zinc absorption mechanisms may ameliorate the clinical manifestations of type II diabetes.

During the last two decades, several biochemicals were found to be involved in the regulation of intestinal zinc absorption. Our laboratory found that prostaglandins[8,9] and arachidonic acid (AA)[10,11] are stimulators of intestinal zinc absorption. Subsequently, L-histidine[12] and testosterone[13] were also found to stimulate intestinal zinc absorption. Others found that citric acid is the chelating agent that makes zinc available for absorption.[14] CYCLO(His-Pro) metabolism is directly related to zinc metabolism.[15] Interestingly, the prostate is the organ that contains the highest amounts of zinc and all of these chemicals.[16-18] Hence, we tested the effects of prostate extract on the intestinal zinc absorption rate and found it to be a more effective stimulator of intestinal zinc absorption than AA or zinc alone.[19] Dietary feeding of rabbit prostate extract plus zinc also improved the clinical manifestations of diabetes in streptozotocin-induced diabetic rats. Dietary feeding of excess zinc did not improve the clinical manifestations of diabetic rats, but feeding prostate extract did. Since adequate zinc was consumed by diabetic rats, it appears that the biochemical constituents including zinc in the prostate improve the clinical condition of diabetes. Thus, we hypothesized that all of these chemicals including zinc influence the cellular function of insulin-requiring tissues. The aim of the present study is to determine whether bovine prostate powder supplemented with 20 mg zinc improves the clinical condition of older men with type II diabetes.

SUBJECTS AND METHODS

Subjects

Forty-eight men with type II diabetes aged 60 to 75 years were recruited from the outpatient clinic at Sepulveda Department of Veterans Affairs (DVA) Medical Center. Twenty-five of the patients were assigned to the test group and 23 to the placebo group. However, only 22 patients in the test group and 18 in the placebo group finished 3 months of study. All subjects were on oral agents for glucose control. The research protocol was approved by the Human Study Subcommittee and subsequently by the Research and Development Committee at Sepulveda DVA Medical Center. Each patient was asked to read and sign a written informed-consent form.

Protocol

Each subject was asked to eat a high-carbohydrate diet for at least 3 days before glucose tolerance testing. Both Pro-Z (Table 1) and placebo gel capsules were made by Banner Pharmacaps (Chatsworth, CA). Test capsules were labeled as B and placebo capsules as A. Patients were asked to choose one treatment with the understanding that either A or B was the placebo, and the person assigning the patients to either the test or the placebo group was blinded. Each patient was asked to come to the hospital on a different date in the morning after an overnight fast. Three test tubes, each containing about 10 mL blood, were drawn from the arm

From the Research and Psychology Services, West Los Angeles Department of Veterans Affairs (DVA) Medical Center, Los Angeles; Geriatric Research Center, Sepulveda DVA Medical Center, North Hills; Departments of Pediatrics, Medicine, and Psychiatry, School of Medicine, Los Angeles, CA; and Department of Biological Sciences, Korean Advanced Institute of Sciences and Technologies, Taejon, Korea.

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Address reprint requests to M.K. Song, PhD, West LA DVA Medical Center, 11301 Wilshire Blvd, Bldg 114, room 205, Los Angeles, CA, 90073.

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Table 1. Chemical Composition of Test Gel Capsule (Pro-Z)

Active ingredients	
Bovine prostate powder	200 mg
Zinc amino acids (20 mg elemental zinc)	100 mg
Excipient	
Safflower seed oil	330 mg
Lecithin	10 mg
Beeswax	10 mg
Soybean shortening oil	40 mg
Hydrogenated soybean oil	10 mg
Shell	
Gelatin	201 mg
Glycerin	112 mg
Water	27 mg
Titanium dioxide	2 mg
FD & C Yellow No. 6	0.732 mg
FD & C Blue No. 1	0.034 mg
FD & C Red No. 40	0.019 mg
Total gel weight	1,042.785 mg

vein of each patient. One tube was used for testing liver, kidney, and lipid panels, the second for measurement of hemoglobin A_{1C} (HbA_{1C}), and the third for determination of insulin, glucose, zinc, and other minerals. Urine samples were also collected from these patients for measurement of various chemicals as measured in the blood. Each patient was then asked to drink 75 g glucose, and blood glucose responses were measured every 30 minutes for 3 hours. Then, the 3-hour area above the fasting glucose concentration (TAFGC) was determined by measuring the mean glucose concentrations for 3 hours above the fasting glucose concentration immediately after the intake of 75 g glucose. Three months later, the same tests were repeated.

Assays

Blood chemistry was measured by standard clinical means. Glucose concentrations in urine samples were measured with a Glucose Analyzer (Yellow Springs Instrument, Yellow Springs, OH). Zinc, magnesium, and calcium concentrations in plasma and urine samples were determined by a Perkin-Elmer (Norwalk, CT) atomic absorption spectrophotometer. Insulin concentrations were determined by the Diabetes Research Laboratory at West LA DVA Medical Center using a radioimmunoassay. Briefly, a standard curve was initially made by adding 200 μL insulin standard solution of known concentration (0, 5, 15, 50, 100, 200, and 400 μIU/mL) to each Ab-Coated tube supplied by Diagnostic Products (Los Angeles, CA). No cross-reactivity with other peptides was identified, and the sensitivity is 1 μIU/mL. After adding 1.0 mL ^{125}I-insulin to every tube containing 200 μL sample or standard solution, the tubes were vortexed and then incubated for 18 to 24 hours at room temperature, and all contents of the tubes were decanted and then counted in a gamma counter. Based on the counts per minute radioactivity, the sample insulin concentrations were calculated by plotting the percent bound against the known insulin concentration: % bound = net cpm/net maximum binding cpm × 100, and net cpm = mean cpm of duplicate tubes of samples − mean cpm of nonspecific binding of tubes.

Statistical Analysis

Paired *t* tests were used for comparison of results from before and after treatment with GraphPad InStat version 1.13 (GraphPad Software, San Diego, CA). Analyses of the major biochemical variables were performed using analysis of covariance (ANCOVA) with each posttreatment measure as the dependent variable and the pretreatment baseline for that day as the covariance[20] (BMDP Statistical Software, Los Angeles, CA). A P value less than .05 was considered statistically significant.

RESULTS

The mean fasting blood glucose in patients given Pro-Z (prostate powder and zinc) for 3 months did not significantly decrease compared with the values before treatment ($P = .14$; Table 2). This appears to be due to seven patients whose blood glucose increased. However, the mean values for blood glucose in the group of patients who had demonstrated decreased blood glucose levels were significantly low compared with before treatment ($P = .038$). In contrast, both blood HbA_{1C} and TAFGC in all patients who were given Pro-Z decreased very significantly ($P < .0003$ and .0005, respectively) compared with the values before treatment. The results of ANCOVA also indicated that the changes in the values for HbA_{1C} and TAFGC in the total test group were very significant ($P = .014$ and .006, respectively). On the other hand, TAFGC values in subjects given placebo increased compared with before treatment, and both fasting glucose and HbA_{1C} levels did not change. In plasma samples from patients given Pro-Z, insulin was decreased 27.6% compared with the values before treatment, showing marginal significance ($P = .079$; Table 3). Plasma zinc increased in the Pro-Z–treated group ($P = .02$) without changing calcium and magnesium concentrations. No changes were shown in the placebo group for all minerals measured. When urinary glucose concentrations were measured in the Pro-Z–treated group, the levels were significantly lower versus before treatment ($P = .0005$; Table 4). Zinc concentrations in the urine samples increased as expected ($P < .0003$). P values for the results of ANCOVA of urine glucose and zinc concentrations were .005 and .002, respectively, compared with the placebo

Table 2. Oral Glucose Tolerance and HbA_{1c} Levels in Type II Diabetic Patients Treated With Pro-Z for 3 Months

Parameter	TAFGC (OGTT) (mg · G/dL/h)	HbA_{1c} (%)	Fasting Glucose (mg/dL)
Pro-Z			
Total group			
Before treatment	140.5 ± 9.2	12.2 ± 0.7	202.2 ± 22.9
After treatment	101.5 ± 8.0	9.5 ± 0.5	169.2 ± 12.2
Difference	39.0 ± 9.6	2.7 ± 0.6	33.0 ± 21.9
No. patients	22	22	22
P	.0005	.0003	.14
Responder group			
Before treatment	141.7 ± 10.3	12.5 ± 0.8	220.9 ± 32.1
After treatment	94.6 ± 7.5	8.9 ± 0.5	156.1 ± 14.2
Difference	47.2 ± 9.8	3.6 ± 0.6	64.8 ± 28.4
No. of patients	19	17	15
P	.0001	<.0001	.038
Placebo			
Before treatment	121.2 ± 8.4	10.4 ± 0.8	166.5 ± 12.3
After treatment	126.4 ± 8.0	10.2 ± 0.6	165.2 ± 11.6
Difference	−5.1 ± 9.4	0.2 ± 0.4	1.3 ± 10.4
No. of patients	18	18	18
P	.59	.59	.90

Abbreviation: OGTT, oral glucose tolerance test.

Table 3. Glucose, Insulin, Zinc, Calcium, and Magnesium Levels in Plasma Samples of Patients Given Either Pro-Z or Placebo

Medication	Glucose (mg/dL)	Insulin (μU/mL)	Zinc (μg/mL)	Calcium (μg/mL)	Magnesium (μg/mL)
Pro-Z (n = 28)					
Before treatment	197 ± 20	21.4 ± 4.4	1.20 ± 0.06	77.0 ± 2.8	16.6 ± 0.5
After treatment	170 ± 9	15.5 ± 1.9	1.39 ± 0.05	76.3 ± 1.5	15.9 ± 0.4‡
Difference	27 ± 20*	5.9 ± 3.4*	−.19 ± 0.06†	0.7 ± 2.7	0.7 ± 0.5*
Placebo (n = 19)					
Before treatment	159 ± 11	13.4 ± 2.2	1.24 ± 0.07	76.3 ± 2.9	16.7 ± 0.7
After treatment	160 ± 13	13.8 ± 2.4	1.30 ± 0.10	80.8 ± 3.6	17.4 ± 0.5
Difference	−1 ± 11	−0.4 ± 2.7	−.06 ± 0.10	−4.5 ± 4.6	0.6 ± 0.9

*P = .1-.05, †P < .001: after treatment *v* before treatment.
‡P < .05, Pro-Z *v* placebo.

group. Calcium and magnesium concentrations in the urine did not change, although some trend to increase was observed.

To determine whether Pro-Z led to any medical side effects, fasting panels of liver, kidney, and lipid biochemicals were analyzed (Tables 5 to 7). Blood lactate dehydrogenase increased 24% in the Pro-Z–treated group ($P < .05$) versus 8% in the control subjects (NS; Table 5). Alanine transaminase concentrations increased 22% in the group given placebo ($P < .005$). No other biochemical changes in liver-function tests were shown in both Pro-Z– and placebo-treated groups. Blood urea nitrogen concentrations decreased 14% in the Pro-Z group ($P < .01$), while those in the placebo group did not change at all (Table 6). Carbon dioxide and glucose concentrations in the blood of the Pro-Z group decreased with marginal significance. No other biochemical changes of the kidney were observed in either group. Interestingly, blood cholesterol and low-density lipoprotein levels decreased with marginal significance in subjects given Pro-Z (Table 7). Although not statistically significant, high-density lipoprotein (HDL) in Pro-Z–treated subjects showed a tendency to higher levels after treatment, whereas levels tended to be lower in the placebo group. The cholesterol to HDL ratio significantly increased in the placebo group. Triglycerides tended to increase in the placebo group and decrease in the Pro-Z group.

DISCUSSION

Diabetic animals and humans are zinc-deficient,[4-6,10,19,21,22] and zinc-deficient animals showed impaired glucose tolerance that can be corrected by zinc supplementation.[23,24] Prostaglandins and arachidonic acid are involved not only in the regulation of intestinal zinc absorption but also in numerous diabetes-related metabolic activities.[25-28] Citric acid stimulates intestinal zinc absorption,[14] and it is present at very high levels in the prostate.[16] Testosterone stimulates intestinal zinc absorption,[13] and plasma levels of this steroid are lower in men with diabetes than in normal men.[29,30] CYCLO(His-Pro) is a major thyrotropin-releasing hormone metabolite and is present in a larger quantity in the prostate than in any other tissue.[17] Its synthesis requires zinc.[15] Since the prostate contains high levels of zinc, prostaglandins, essential fatty acids, citric acids, testosterone, CYCLO(His-Pro) and amino acids and these constituents are all involved in the control of intestinal zinc absorption,[19] it appears that all of the constituents contained in the prostate may act synergistically to regulate zinc metabolism in the organ cells of patients with diabetes. On the other hand, zinc plays a key role in insulin production by the pancreas[31] and glucose utilization by muscle and fat cells.[2,32] Thus, the ability of the organ cells to use glucose is impaired in the zinc-deficient state.[32] Our previous studies showed that prostate constituents including zinc may synergistically act to improve the clinical manifestations of diabetes in rats,[19] and the present data partially confirm such a relationship. However, the data in Tables 2 to 4 show that bovine prostate contains some active ingredients that affect the pathophysiology of diabetes. We are currently identifying such chemicals for the treatment of diabetic animals.

The treatment for diabetic patients has been either oral agents or insulin. The sulfonylurea derivatives are commonly used oral agents to treat diabetes in the United States. These agents simply stimulate insulin release from pancreatic β cells. The treatment of diabetes by these agents is strictly to control blood glucose levels. The best treatment for type II diabetes is to stimulate glucose utilization by muscle and fat tissue. At present, two hypoglycemic agents (metformin and troglitazone) for such treatment are available. Although the mechanisms are

Table 4. Glucose, Zinc, Calcium, and Magnesium Levels in Urine Samples of Patients Given Either Pro-Z or Placebo

Medication	Glucose (mg/dL)	Zinc (μg/mL)	Calcium (μg/mL)	Magnesium (μg/mL)
Pro-Z (n = 31)				
Before treatment	1,249 ± 236	0.80 ± 0.07	47.0 ± 4.4	72.0 ± 6.2
After treatment	378 ± 82	1.36 ± 0.14	51.3 ± 5.6	82.1 ± 8.7
Difference	871 ± 240*	0.44 ± 0.14†	4.3 ± 5.3	10.1 ± 10.2
Placebo (n = 18)				
Before treatment	877 ± 175	0.81 ± 0.10	49.1 ± 7.9	65.5 ± 6.0
After treatment	778 ± 329	0.75 ± 0.08	49.2 ± 7.1	64.0 ± 9.6
Difference	99 ± 365	0.06 ± 0.12	0.1 ± 8.5	1.5 ± 7.6

*P < .01, after treatment *v* before treatment.
†P < .001, after treatment *v* before treatment.

Table 5. Effect of Pro-Z on Concentrations of Biochemicals Related to Liver Function

Biochemical	Medication	No.	Before Treatment	After Treatment	P
Alkaline phosphatase (U/L)	Placebo	13	83.0 ± 5.6	89.0 ± 5.6	.1193
	Pro-Z	14	88.8 ± 8.9	83.2 ± 8.8	.3632
Alanine transaminase (U/L)	Placebo	12	31.8 ± 1.9	38.8 ± 1.7	.0015*
	Pro-Z	11	30.2 ± 2.2	33.9 ± 3.1	.2232†
Lactic dehydrogenase (U/L)	Placebo	13	470.1 ± 34.7	515.2 ± 22.0	.1612
	Pro-Z	12	388.3 ± 43.5	483.2 ± 17.5	.0367*
Total blood protein (g/dL)	Placebo	13	7.19 ± 0.11	7.00 ± 0.09	.1176
	Pro-Z	14	6.86 ± 0.11	6.81 ± 0.15	.7368
Albumin (g/dL)	Placebo	13	3.85 ± 0.07	3.98 ± 0.06	.1356
	Pro-Z	14	3.99 ± 0.07	3.89 ± 0.08	.3400
Total bilirubin (mg/dL)	Placebo	13	0.85 ± 0.14	0.78 ± 0.12	.4801
	Pro-Z	14	0.74 ± 0.07	0.74 ± 0.06	.99

*$P < .05$, after treatment *v* before treatment.
†$P < .05$, Pro-Z *v* placebo.

Table 6. Effects of Pro-Z on Concentrations of Biochemicals Related to Kidney Function

Biochemical	Medication	No.	Before Treatment	After Treatment	P
Blood urea nitrogen (mg/dL)	Placebo	15	18.2 ± 0.9	18.9 ± 2.2	.6891
	Pro-Z	14	20.9 ± 1.6	18.0 ± 1.7	.0068*
Sodium (mEq/L)	Placebo	15	140.7 ± 0.6	140.7 ± 0.8	.9323
	Pro-Z	13	137.5 ± 1.2	138.2 ± 0.9	.3332
Potassium (mEq/L)	Placebo	15	4.27 ± 0.10	4.17 ± 0.12	.3008
	Pro-Z	12	4.36 ± 0.14	4.37 ± 0.13	.9623
Chloride (mEq/L)	Placebo	15	104.3 ± 0.76	103.3 ± 1.03	.3804
	Pro-Z	17	101.2 ± 1.09	101.2 ± 0.95	.9596
Carbon dioxide (mEq/L)	Placebo	15	26.86 ± 0.82	25.45 ± 0.71	.1289
	Pro-Z	15	28.07 ± 0.77	27.20 ± 1.02	.0718†
Glucose (mg/dL)	Placebo	19	171.3 ± 12.4	161.6 ± 11.7	.405
	Pro-Z	14	223.6 ± 30.1	176.0 ± 11.6	.0749†
Creatinine (mg/dL)	Placebo	15	1.18 ± 0.10	1.23 ± 0.17	.6293
	Pro-Z	14	1.16 ± 0.05	1.14 ± 0.04	.3870

*$P < .05$, after treatment *v* before treatment.
†$P < .05$, Pro-Z *v* placebo.

not known, metformin reduces hepatic glucose overproduction and increases insulin sensitivity. However, treatment of patients with metformin alone is not likely to help either with or without sulfonylurea therapy when blood glucose is higher than 280 mg/dL.[33] Troglitazone also increases the insulin sensitivity of target tissues.[34,36] However, the effects of troglitazone on insulin sensitivity are limited due to small decreases of blood glucose, when it shows some side effects.

Similar to these agents, Pro-Z treatment also stimulated glucose utilization by muscle and fat tissue (Table 2), when blood insulin decreased (Table 3). Although the exact mechanism is not known, it is apparent that Pro-Z reduced blood glucose and HbA_{1C} and the mean values for TAFGC. When glucose utilization is improved, blood insulin decreases due to the feedback regulatory mechanisms of insulin synthesis. A decrease in the mean ratio of insulin to glucose (10.86 to 9.12 μU insulin/mg glucose) supports improved insulin action and less insulin resistance. The mean ratio in the placebo group showed a tendency to increase (8.42 to 8.63 μU insulin/mg glucose). Since high blood glucose stimulates more insulin secretion by pancreatic β cells (Song MK, Levin SR, unpublished data, October 1997), the data in Table 2 support an improvement of glucose control in diabetic patients.

A decreased insulin concentration also stimulates liver glucose production. Therefore, it is apparent that Pro-Z enhances glucose utilization in organ tissues even though blood glucose did not decrease substantially. The fact that urine glucose concentrations decreased very significantly (Table 4) further supports the role of Pro-Z in the control of glucose metabolism. When blood glucose increases to 180 mg/dL or higher, glucose is detected in the urine. Most diabetic patients in the study group showed high urinary glucose concentrations. Thus, an improvement of glucose utilization by the organ tissue may appear as a reduced urinary glucose concentration (Table 4). The most commonly used antidiabetic agent (glyburide) showed an increased cardiovascular mortality.[33] However, Pro-Z did not have any toxic effects (Tables 5 to 7). Although the exact mechanisms are not known, it appears that Pro-Z improves cholesterol metabolism and glucose control in type II diabetes. The data (Tables 2 to 4) do not show the identity of the chemical constituents in the prostate that improve the clinical condition of diabetic patients and the mechanisms by which the disease is ameliorated. However, the data do show that active ingredients influencing the pathophysiology of diabetes are present in the bovine prostate.

Table 7. Effects of Pro-Z on Concentrations of Biochemicals Related to the Lipid Profile

Biochemical	Medication	No.	Before Treatment	After Treatment	P
Triglyceride (mg/dL)	Placebo	11	254.4 ± 42.1	275.3 ± 39.4	.3626
	Pro-Z	8	256.3 ± 107.1	224.4 ± 44.1	.7742
Low-density lipoprotein cholesterol (mg/dL)	Placebo	11	104.1 ± 10.7	113.6 ± 10.9	.2921
	Pro-Z	9	131.8 ± 11.1	120.3 ± 7.0	.0546†
Cholesterol (mg/dL)	Placebo	11	194.7 ± 11.3	201.0 ± 12.7	.3813
	Pro-Z	9	212.7 ± 17.8	194.8 ± 8.3	.0770†
HDL cholesterol (mg/dL)	Placebo	11	39.7 ± 3.8	32.3 ± 1.8	.0864†
	Pro-Z	8	31.9 ± 2.2	34.6 ± 2.4	.4606
Cholesterol/HDL ratio	Placebo	11	5.10 ± 0.28	6.48 ± 0.60	.0321*
	Pro-Z	8	6.10 ± 0.58	6.33 ± 0.52	.5528

*$P < .05$, after treatment *v* before treatment.
†$P < .05$, Pro-Z *v* placebo.

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