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Effects of Pinitol on Glycemic Control, Insulin Resistance and Adipocytokine Levels in Patients with Type 2 Diabetes Mellitus

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Key Words
Pinitol · Type 2 diabetes mellitus · Glycemic control · Insulin resistance · Adipocytokine levels

Abstract
Background: Pinitol is thought to mediate insulin action and improve insulin resistance. We evaluated the effects of pinitol on glycemic control, insulin resistance and adipocytokine levels in type 2 diabetic patients. ***Material and Method:*** A total of 66 patients with type 2 diabetes who had been taking oral hypoglycemic agents for at least 3 months were enrolled and randomized to receive pinitol (n = 33) or matching placebo (n = 33). All subjects took 1,200 mg pinitol or placebo and maintained their current oral hypoglycemic agents throughout the study. ***Results:*** Mean HbA1c, fasting plasma glucose, and HOMA-IR were significantly lowered more in patients taking pinitol than in those given a placebo. Patients who had an HbA1c over 8.0% showed a greater reduction ($p < 0.01$) than those who had an HbA1c below 8.0% ($p = 0.16$). In addition, in the group of patients with a HOMA-IR over 2.5, there was a significant decrease in HbA1c compared to that in the group of patients with a HOMA-IR below 2.5. There were no differences in the changes in adiponectin, FFA and CRP between the two groups. ***Conclusions:*** Pinitol can mediate insulin action to improve glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus, especially in patients with insulin resistance.

Introduction

Type 2 diabetes mellitus is characterized by impaired insulin secretion, peripheral insulin resistance, and excessive hepatic glucose production, which are the targets of the oral agents. Agents that can improve insulin resistance are metformin and thiazolidinedione.

Pinitol which is a monosaccharide found in high concentrations in legumes and soy beans is thought to mediate insulin action and improve insulin resistance. Pinitol is converted to D-chiro-inositol (DCI) in the body, and DCI may be a component of an inositol phosphoglycan (IPG). IPGs are potentially important post-receptor mediators of insulin action [1, 2]. It was reported that the administration of pinitol reduced blood glucose levels in streptozotocin-induced diabetic rats [3, 4], and pinitol combination therapy with other oral hypoglycemic

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agents decreased fasting glucose, postprandial glucose and hemoglobin A1c in type 2 diabetic patients [5]. We previously conducted a clinical study to determine the efficacy and safety of pinitol in type 2 diabetic patients. Pinitol treatment (400 mg three times a day for 12 weeks) was effective and safe in type 2 diabetic patients who had treated with oral hypoglycemic agents [6]. DCI increased the rate of disappearance of plasma glucose and insulin in hyperinsulinemic monkeys [7], which suggested that it could improve insulin resistance and glucose metabolism. However, another study showed that insulin sensitivity did not increase after pinitol treatment in obese individuals with mild type 2 diabetes [8]. Thus, the effect of pinitol on insulin action and insulin resistance remains controversial.

Plasma adipocytokine levels are correlated with insulin sensitivity and resistance [9]. Adiponectin is the most important factor for increasing insulin sensitivity, while factors such as leptin, resistin and C-reactive protein are known to be related to the increase of insulin resistance [10]. It could be expected that pinitol treatment would alter adipocytokine levels if pinitol could improve insulin sensitivity. In a previous study, however, pinitol treatment did not alter adipocytokine levels [5]. The effect of pinitol on adipocytokine levels also remains unknown.

The aim of the present study was to evaluate the effects of pinitol on glycemic control, insulin resistance and adipocytokine levels in patients with type 2 diabetes mellitus.

Materials and Methods

Subjects

From March 2005 to August 2005, 66 patients from Eulji Medical Center who were diagnosed with type 2 diabetes and who had been taking oral hypoglycemic agents for at least 3 months were enrolled. Entry criteria for this study included age between 20 and 75 years old, hemoglobin A1c of more than 6.5%, and informed consent. Patients who had a past history of diabetic ketoacidosis or hyperosmolar hyperglycemic state within the previous 3 months were excluded. In addition, people who had been treated with insulin, were pregnant, had renal dysfunction, had hepatic dysfunction, had significant diabetic cardiovascular disease or had significant diabetic complications were excluded. The Institutional Review Board of Eulji Medical Center approved the protocol.

Materials and Study Design

Pinitol (3-O-methyl-chiro-inositol) was purchased from Biosolutions (Daejeon, Korea). This study was a double-blind, placebo-controlled study. Patients were randomized to receive pinitol or a matching placebo. All subjects took 1,200 mg (400 mg three times a day) of pinitol (n = 33) or a placebo (n = 33), which was made of whey protein, and maintained their current oral hypoglycemic agents throughout the study. We calculated the sample size of this study as follows:

Level of significance, $\alpha = 0.05$

Type 2 error $\beta = 0.20$

μ_t: ΔHbA1c (HbA1c after pinitol treatment – HbA1c before treatment)

μ_c: ΔHbA1c (HbA1c after placebo treatment – HbA1c before treatment).

The significant difference of ΔHbA1c ($\mu_t - \mu_c$) between two treatment was 1.1 and SD in the group was 1.6 as previous studies results were considered.

$$\text{Sample size, } n = \frac{\left(Z_\alpha + Z_\beta\right)^2 \left(\delta_t^2 + \delta_c^2\right)}{\left(\mu_t - \mu_c\right)^2}$$

Biochemical Parameters

The following parameters of each patient were recorded and analyzed: sex, age, height, weight, body mass index [BMI, weight (kg)/height (m^2)], systolic/diastolic blood pressure, and current hypoglycemic agents being used. Blood samples were collected before and after the 12-week treatment for measurements of HbA1c, fasting plasma glucose, 2-hour postprandial glucose, insulin, C-peptide, C-reactive protein (CRP), and adipocytokine (adiponectin, leptin, resistin, free fatty acid) levels.

Plasma glucose was measured with hexokinase assay [Glucose II (HK) Reagents, Bayer, USA]. Plasma HbA1c (VARIANT II Hemoglobin A1c Program), plasma insulin (Roche, Germany) and C-peptide (Roche, Germany) were measured by radioimmunoassay. Plasma adiponectin and leptin concentrations were determined by radioimmunoassay (LINCO Research, USA) and plasma resistin concentrations were determined by enzyme-linked immunosorbent assay (KOMED, Korea). The free fatty acid (Wako, Japan) and CRP (Bayer, USA) levels were measured with commercially available kits.

Statistical Analysis

Statistics were calculated with StatView for Windows (version 5.0; SAS Institute, Cary, N.C., USA). Values before and after treatment in a given individual were analyzed using paired-samples t tests. Multiple regression analysis were performed for determining the relationship between changes in HbA1c and other variables (pretreatment HbA1c, gender, BMI, and family history of diabetes mellitus). All data were expressed as the mean ± SD. $p < 0.05$ was considered statistically significant.

Results

Clinical Characteristics and Metabolic Measurements

Of 82 patients screened, 66 were randomly allocated to study groups (33 to the pinitol group, 33 to the placebo group). 31 patients in the pinitol group and 30 patients in the placebo group completed the study and 5 patients withdrew their consent. The clinical characteristics of patients at baseline are summarized in table 1. The participants included 20 men (30.3%) and 46 women (67.7%).

Table 1. Baseline characteristics of the study population

	Pinitol (n = 33)	Placebo (n = 33)
Sex, male/female	9/24	11/22
Age, years	56.3 ± 9.8	52.9 ± 10.5
BMI	25.30 ± 3.25	26.13 ± 3.03
Systolic BP, mm Hg	127.18 ± 17.20	129.97 ± 12.01
Diastolic BP, mm Hg	76.30 ± 17.96	76.03 ± 7.19
HbA1c, %	8.38 ± 1.69	8.41 ± 1.24
FPG, mg/dl	185.64 ± 103.68	171.91 ± 64.60
PP2hrG, mg/dl	210.92 ± 69.77	203.67 ± 65.41
C-peptide, ng/ml	3.68 ± 2.51	3.42 ± 2.06
Insulin, IU/l	18.49 ± 18.26	16.05 ± 16.06
Triglyceride, mg/dl	182.15 ± 99.38	272.03 ± 312.79
Total cholesterol, mg/dl	177.64 ± 41.16	195.97 ± 36.22
LDL-cholesterol, mg/dl	102.76 ± 34.18	113.76 ± 48.93
HDL-cholesterol, mg/dl	39.91 ± 10.03	41.48 ± 8.40
Adiponectin, μg/ml	4.34 ± 2.72	3.68 ± 2.00
Leptin, ng/ml	9.63 ± 5.40	10.52 ± 6.12
Resistin, ng/ml	5.27 ± 4.25	5.11 ± 3.87
Free fatty acid, μmol/l	520.91 ± 262.68	532.76 ± 327.27
C-reactive protein, mg/dl	0.17 ± 0.24	0.12 ± 0.19
Number of patients taking hypoglycemic agents		
Sulfonylurea	33	33
Biguanides	21	26
Alpha-glucosidase inhibitor	13	8
Meglitinides	0	1

Although there were more women than men, there was no significant difference between the two study groups. The mean age of the patients was 54.6 ± 10.27 years. The pinitol and placebo groups were similar in age, BMI, blood pressure, HbA1c, fasting plasma glucose, 2-hour postprandial glucose, insulin, C-peptide, lipid profile and current hypoglycemic agents. In addition, there were no differences in plasma adiponectin, leptin, resistin, free fatty acid, and C-reactive protein between the pinitol and placebo groups before treatment.

Effects on Glucose Control

Table 2 shows changes (values after treatment – values before treatment, Δ) of parameters of glucose control. Mean HbA1c was lowered more in patients randomly assigned to the pinitol group. In the pinitol group, both plasma glucose and postprandial glucose levels were lowered; however, only the fasting plasma glucose level change was significant. HOMA-IR, which is an index of insulin resistance, was lowered more in the pinitol group. There were no significant differences in the changes in C-peptide and insulin between the placebo and pinitol

Table 2. Changes (Δ) in the parameters of glucose control

	Pinitol	Placebo	p
HbA1c, %	−0.65 ± 0.92	−0.01 ± 0.79	<0.01
FPG, mg/dl	−52.58 ± 80.75	−2.21 ± 55.88	<0.01
PP2hrG	−10.50 ± 59.21	15.94 ± 76.05	0.30
C-peptide	−0.82 ± 2.74	−0.74 ± 2.50	0.89
Insulin	−4.88 ± 19.33	−6.55 ± 14.43	0.69
HOMA-IR	−6.08 ± 8.97	−0.71 ± 10.67	<0.01

groups. Patients who had an HbA1c over 8.0% showed a greater level of reduction ($p < 0.01$) than those who had an HbA1c below 8.0% ($p = 0.16$) (fig. 1). In addition, in the group of patients with a HOMA-IR over 2.5, there was a significant decrease in HbA1c compared to that in the group of patients with a HOMA-IR below 2.5 ($p = 0.26$) (fig. 2).

Effects on Plasma Adipocytokines

Table 3 shows changes (values after treatment – values before treatment, Δ) in adipocytokine concentrations after treatment with pinitol and placebo. There were no differences in the changes of adiponectin, FFA, and CRP between the pinitol and placebo groups after 12-week treatment. Leptin was lowered significantly in the placebo group ($p < 0.05$).

Predictors of Response to Treatment

Multiple regression analysis showed that the pre-treatment HbA1c level was a significant predictor of favorable decline in HbA1c after pinitol treatment ($r = -0.65$; $p < 0.01$). No significant correlation was found between changes in HbA1c and gender ($r = 0.41$; $p = NS$), age ($r = 0.01$; $p = NS$), BMI ($r = 0.03$; $p = NS$), or family history of diabetes mellitus ($r = -0.13$; $p = NS$) in the pinitol group before treatment.

Discussion

This randomized placebo-controlled study revealed that pinitol improved glucose control by significantly lowering HbA1c, fasting plasma glucose and HOMA-IR. Postprandial glucose and C-peptide levels also tended to decrease, although there was no statistical significance. Pinitol treatment reduced HbA1c more in patients who had an HbA1c over 8.0% than in those who had an HbA1c below 8.0%. In addition, in patients with a HOMA-IR

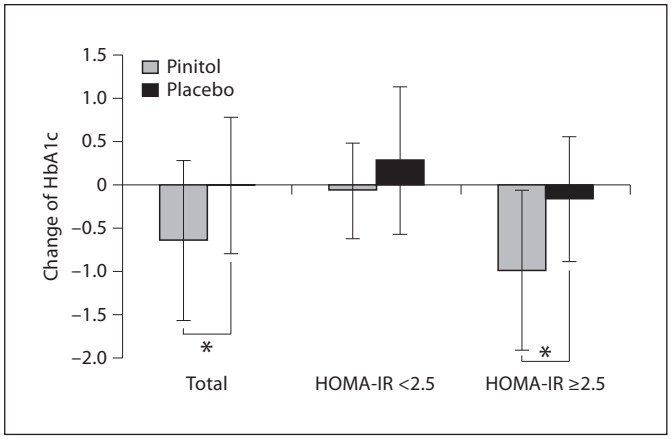

Fig. 1. Change in HbA1c in each group divided by the baseline HOMA-IR level. * $p < 0.01$, pinitol (grey bar) vs. placebo (black bar).

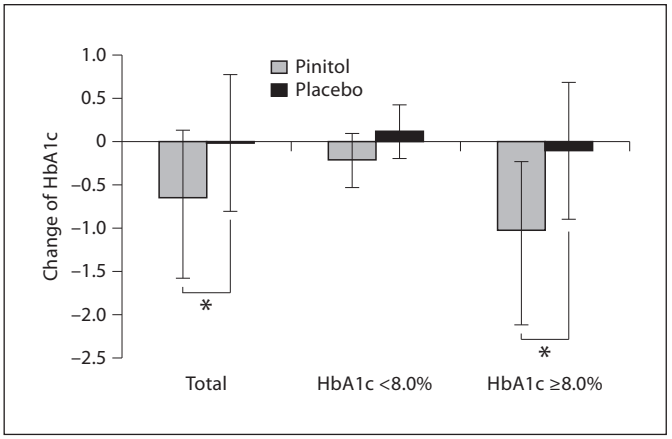

Fig. 2. Change in HbA1c in each group divided by the baseline HbA1c level. * $p < 0.01$, pinitol (grey bar) vs. placebo (black bar).

Table 3. Changes (Δ) in adipocytokine concentrations after pinitol and placebo treatment

	Pinitol	Placebo	p
Adiponectin, μg/ml	3.11 ± 4.72	1.31 ± 2.35	0.07
Leptin, ng/ml	–0.84 ± 6.85	–4.71 ± 6.85	<0.05
Resistin, ng/ml	2.38 ± 6.09	3.49 ± 6.89	0.05
Free fatty acid, μmol/l	160.75 ± 339.56	105.53 ± 381.30	0.54
C-reactive protein, mg/dl	0.58 ± 3.25	0.08 ± 0.22	0.39

over 2.5, there was a significant decrease in HbA1c compared to that in patients with a HOMA-IR below 2.5. These results suggest that pinitol is more effective in patients with a higher glucose level and more insulin resistance.

IPGs are thought to be important putative intracellular mediators of insulin action [1, 2]. Pinitol has been identified as a separate class of IPGs as a monomethylated form of DCI. DCI-containing phosphoglycan has been shown to activate both glycogen synthase phosphatase and pyruvate dehydrogenase phosphatase [11], which are involved in activating glucose metabolism by acting on the insulin signaling pathway. The role of DCI in insulin action has been investigated in patients with diabetes. Low urinary excretion and low tissue levels of chiro-inositol were found in patients with type 2 diabetes compared to those in normal subjects [12, 13]. Cheang et al. [14] also demonstrated that pinitol treatment increased glucose-stimulated DCI-IPG release and improved insulin sensitivity in women with polycystic ovary syndrome. One clinical study showed that 12-week pinitol treatment significantly decreased fasting glucose, postprandial glucose levels, and hemoglobin A1c in patients with uncontrolled type 2 diabetes [5]. In yet another study, pinitol decreased mean fasting plasma glucose, insulin, HbA1c, and HOMA-IR, and improved the lipid profile [15].

Pinitol could improve insulin sensitivity since pinitol treatment decreased HOMA-IR and was more effective in patients with insulin resistance. Pinitol could be an antidiabetic medicine and insulin sensitizer like thiazolidinedione and metformin. To date, the exact mechanisms for improving insulin sensitivity are unknown. It could be surmised from previous studies and this study that pinitol is converted to DCI, which increases IPG and activates the insulin signaling pathway.

Adipocytes function not only as a fat depot, but also as an endocrine organ that releases various hormones in response to specific extracellular stimuli or changes in metabolic status. These secreted proteins, which include leptin, resistin, adiponectin, TNF, IL-6, and others, carry out a variety of diverse functions and are collectively referred to as adipocytokines [9]. Adiponectin regulates energy balance. An adiponectin deficiency might contribute to the development of insulin resistance and type 2 diabetes mellitus [16, 17]. Resistin, IL-6, and TNF are adipocytokines that might be connected to insulin resistance [18]. Circulating levels of leptin reflect the amount of energy stored in adipose tissue [19]. Insulin-resistant patients with type 2 diabetes mellitus have

higher serum leptin levels, independent of body fat mass [20]. Thiazolidinediones, which are insulin-sensitizing agents, have beneficial effects on plasma adipocytokine levels [21, 22]. We expected that pinitol would increase adiponectin level and decrease resistin, leptin, FFA and CRP. In a previous study, however, pinitol treatment did not change plasma adiponectin, leptin, FFA and CRP. Our study also showed that pinitol treatment did not change the adipocytokine levels significantly; only leptin was lowered more significantly in the placebo group. It is possible that 12 weeks is not long enough for the adipocytokine levels to change and that other factors, such as body weight, gender, age, hormones, and cytokine levels, also contribute to the regulation of adipocytokines.

In summary, the results of the present study support the view that pinitol can mediate insulin action to improve glycemic control and insulin sensitivity in patients with type 2 diabetes mellitus, especially in patients with insulin resistance. Further studies are needed to elucidate the mechanism of improvement of glycemic control and insulin sensitivity and to assess the effect on adipocytokines after a longer duration treatment. And these studies could have the meaning to find new drugs improving insulin sensitivity.

Disclosure Statement

There are no conflicts of interest.

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