Single-Dose Pinitol Ingestion Suppresses Post-Prandial Glucose Levels: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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Abstract
Limited studies have demonstrated that chronic consumption of pinitol improved glucose tolerance, and single-dose ingestion (0.6 g) 60 minutes prior to meals suppressed postprandial glucose levels in patients with type 2 diabetes mellitus. However, higher doses (6 g) were required in healthy people who ingested pinitol with a meal. This randomized, double-blind, placebo-controlled, crossover trial was conducted to clarify the effect of 0.6 g of pinitol with a meal on postprandial blood glucose levels in healthy adults. Twenty volunteers aged 18 to 25 years participated in this study. Participants visited the laboratory after an overnight fast. After measuring fasting blood glucose levels (FBG), they consumed test food (0.6 g of pinitol or placebo) and then ate breakfast (577 kcal; protein 14.0 g; fat 5.6 g; and carbohydrate 117.7 g). Blood glucose levels were measured immediately after eating and at 30, 60, 90, and 120 minutes after breakfast. Participants’ mean FBG level was 102.6 ± 8.2 mg/dL. Participants were categorized by their FBG as normal (n = 5; ≤99 mg/dL) or impaired glucose tolerance (IGT) (n = 15; 100-125 mg/dL). The incremental area under the curve of blood glucose over 120 minutes after the meal was significantly suppressed by pinitol in the IGT group (P < 0.05), but not in the normal group. Therefore, pinitol was considered to maintain postprandial blood glucose levels in healthy people with IGT, and may contribute to the prevention of type 2 diabetes.

Keywords
diabetes mellitus, impaired glucose tolerance, food substance, prevention, inositol, bioactivity

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In 2017, 425 million adults worldwide were estimated have diabetes mellitus, and this number is expected to increase to 693 million by 2045.1 Even in an asymptomatic population, high glucose concentrations 2 hours after a glucose load significantly elevate cardiovascular mortality, independent of fasting blood glucose (FBG) levels.2 Therefore, strategies are needed to maintain postprandial glucose levels.

Pinitol (3-O-methyl-D-chiro-inositol) is a methylated derivative of D-chiro-inositol present in various plants used as herbal medicines, such as Mesembryanthemum crystallinum in South Africa,1 bougainvillea in India, Siberian ginseng in Korea, and Palo azul in Paraguay.3 Chronic consumption (13 weeks) of pinitol (0.6 g/d) has been shown to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).5 In terms of a single dose, ingestion of 0.6 g of pinitol 60 minutes prior to an intake of cooked white rice containing 50 g of available carbohydrate was shown to suppress postprandial glucose levels in patients with T2DM,6 and 6 g of pinitol ingested with 51.0 g of available carbohydrate was shown to suppress postprandial glucose levels in healthy adults.7 Therefore, pinitol appears to be a useful food substance in controlling postprandial increases in blood glucose levels.

However, the information on the timing and amount of pinitol ingestion is limited to the above 2 reports.6,7 Therefore, we performed a randomized, double-blind, placebo-controlled, crossover study to clarify the effects of 0.6 g of pinitol with a meal on postprandial blood glucose levels in healthy adults.

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Table 1 shows participants’ age, height, body weight, and body mass index by sex. Participants’ mean FBG level was 102.6 ± 8.2 mg/dL. Mean FBG levels in 15 participants were ≥100 mg/dL, although none was classified as having diabetes (≥126 mg/dL). Most (n = 15) of the participants’ FBG levels were categorized as “B: Slightly abnormal” or “C: Requires follow-up” according to the criteria of the Japan Society of Ningen Dock (revised on April 1, 2018).8 The “B: Slightly abnormal” and “C: Require follow-up” groups were collectively defined as the impaired glucose tolerance (IGT) group. Participants with FBG levels ≤99 mg/dL (n = 5) were considered the normal group.

The incremental areas under the curve of postprandial glucose levels over 120 minutes (iAUC120) was smaller in the pinitol group than in the placebo group (P < 0.05) (Figure 1a). When stratified by normal (n = 5) and IGT (n = 15) groups, the iAUC inhibitory effect of pinitol was significant in the IGT group (P < 0.05) but not in the normal group (Figure 1b).

The glucose kinetics in the IGT group demonstrated that pinitol led to consistently lower mean glucose levels than placebo at 120 minutes after the meal, although differences were not significant at any time point (Figure 2).

In the present study, 0.6 g of pinitol was shown to suppress iAUC120 in Japanese healthy participants. However, mean FBG levels in 15 participants were ≥100 mg/dL, although none was classified as having diabetes (≥126 mg/dL). Most (n = 15) of the participants’ FBG levels were categorized as “B: Slightly abnormal” or “C: Requires follow-up” according to the criteria of the Japan Society of Ningen Dock (revised on April 1, 2018).8 (Table 2). The “B: Slightly abnormal” and “C: Require follow-up” groups were collectively defined as the impaired glucose tolerance (IGT) group. Participants with FBG levels ≤99 mg/dL (n = 5) were considered the normal group.

The incremental areas under the curve of postprandial glucose levels over 120 minutes (iAUC120) was smaller in the pinitol group than in the placebo group (P < 0.05) (Figure 1a). When stratified by normal (n = 5) and IGT (n = 15) groups, the iAUC inhibitory effect of pinitol was significant in the IGT group (P < 0.05) but not in the normal group (Figure 1b).

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In the present study, 0.6 g of pinitol was shown to suppress iAUC120 in Japanese healthy participants. However, mean FBG levels in 15 participants were ≥100 mg/dL in 15 of 20 participants; these participants were classified as having IGT, although they were not diagnosed with T2DM. A previous study showed that when healthy people ate meals, 6 g of pinitol was required to suppress postprandial blood glucose levels, and 4 g was considered ineffective.7

The iAUC120 in this study showed no significant difference between pinitol and placebo when stratified only for those with FBG levels ≤99 mg/dL; this finding is in accordance with a previous study.7 Therefore, it was confirmed that 0.6 g of pinitol ingested with food did not affect postprandial blood glucose levels in healthy individuals with a FBG ≤99 mg/dL.

One study showed that 1.2 g of pinitol ingested 60 minutes before a meal significantly suppressed blood glucose levels at 90 to 120 minutes and iAUC over 240 minutes after a meal.6 That study also assessed 1.2 g of pinitol with meals, although findings showed postprandial blood glucose levels did not significantly differ up to 240 minutes after the meal among patients who received pinitol vs those who received placebo. That study compared 6 conditions, including controls. Thus, statistical significance in the results may have been missed due to the complexity of the experimental settings requiring multiple comparisons of many different pairs.

In the present study, in the IGT group, 0.6 g of pinitol significantly suppressed iAUC120 compared with placebo, and the estimated marginal means of postprandial blood glucose levels were consistently lower than placebo, although differences did not reach statistical significance. These results may indicate that a lower dose of pinitol suppresses postprandial blood glucose levels in healthy individuals with IGT.

FBG levels of participants in this study showed that 75% (15 of 20) had IGT despite the fact that they were young and none had been previously identified as having IGT. Recently, a high prevalence of high blood sugar levels (HbA1c > 5.5%) has been reported in young Japanese people aged 20 to 39 years.9-11 Thus, glucose tolerance of young people should be carefully assessed and controlled.

The mechanism by which pinitol suppresses postprandial blood glucose elevation is not clear, but a model that suggests the relationship between insulin signal and pinitol has been proposed.4 A few decades ago, skeletal muscle/liver extracts of rats injected with insulin were reported to contain a substance that inhibits protein kinase A and activates glycogen synthase.12 Subsequently, another group independently reported that a low

| Table 1. Characteristics of Participants. | Total (n = 20) | Male (n = 12) | Female (n = 8) |
|-------------------------------------------|---------------|---------------|---------------|
| Age (years) | 20.7 ± 1.5 | 20.8 ± 1.6 | 20.5 ± 1.4 |
| Height (cm)  | 170.1 ± 7.5 | 173.8 ± 5.7 | 164.6 ± 6.6 |
| Body weight (kg) | 63.5 ± 12.1 | 69.5 ± 11.6 | 54.4 ± 5.7 |
| BMI (kg/m²) | 21.8 ± 2.8 | 23.0 ± 2.9 | 20.0 ± 1.1 |

| Table 2. Categories for Fasting Blood Glucose Levels According to the Criteria of the Japan Society of Ningen Dock (Revised on April 1, 2018). |
|-----------------------------------------------|
| Categories | Fasting blood glucose (mg/dL) | n | Male/Female |
| A: Normal | ≤99 | 5 | 5/0 |
| B: Slightly abnormal | 100-109 | 12 | 5/7 |
| C: Requires follow-up | 110-125 | 3 | 2/1 |
| D: Medical care needed | ≥126 | 0 | - |
molecular weight substance that activates pyruvate dehydrogenase phosphatase is produced by plasma membranes of rat adipocytes when stimulated with insulin. These studies led to the concept of a second messenger that conveys the insulin signal. Larner et al identified the pinitol-galactosamine chelated to ionic manganese as the insulin second messenger (INS-2) from the insulin-stimulated cattle liver, and showed that INS-2 lowered blood glucose levels in streptozotocin-induced diabetic rats. Larner et al proposed the following model: INS-2 is produced from pinitol released from glycosylphosphatidylinositol by insulin-activated phospholipase D, then INS-2 activates glycogen synthase through activation of protein phosphatase 2Cz, as well as migrates to mitochondrion to activate pyruvate dehydrogenase (PDH) phosphatase, which then activates PDH. In the present study, as well as in the previous study, pinitol ingested with a meal suppressed the increase in blood glucose levels at 30 to 60 minutes after the meal. However, further study is warranted to clarify how the effect of pinitol taken with meals should be accounted for in the model proposed by Larner et al.4

The present study demonstrated that the ingestion of 0.6 g of pinitol with a meal significantly suppressed postprandial
glucose levels in healthy individuals with IGT. Previous studies showed similar results with a higher dose of pinitol: 1.2 g (60 minutes prior to meal) for patients with T2DM and 6.0 g for healthy volunteers. The participants in the previous study were patients with T2DM aged 60.3 ± 3.1 (mean ± SEM) years and healthy volunteers aged 32.5 ± 7.0 (mean ± SD), with ages ranging from 18 to 65 years old. In contrast, the age of participants in this study was 20.7 ± 1.5 (mean ± SD), with a range of 18 to 24 years. In this study, the small variation in glucose metabolic capacity in younger participants may have contributed to the effect of a low dose of pinitol on IGT.

There were some limitations to this study. First, the number of participants was small. In addition, although participants included 20 healthy individuals, 15 were shown to have IGT. As a result, the effect of pinitol was not significant in healthy individuals with FBG ≤99 mg/dL, but was significant in participants with IGT (100 ≤ FBG < 126 mg/dL). The age range of participants in this study was 18 to 24 years old, and their variation of glucose metabolic capacity was expected to be small, but this was not confirmed directly via an oral glucose tolerance test or the homeostatic model assessment of insulin resistance. Further studies examining glucose metabolic capacity and including more participants are needed to clarify the effect of pinitol.

Ingestion of 0.6 g of pinitol with a meal significantly suppressed the increase in postprandial blood glucose in healthy participants. The effect was not significant in participants with an FBG ≤99 mg/dL; but was significant in participants with IGT (100 ≤ FBG < 126 mg/dL). Therefore, pinitol is considered to maintain postprandial blood glucose levels in healthy people with IGT. As such, it may contribute to the prevention of diabetes.

**Experimental**

**Participants**

Participants (n = 20) were healthy, non-athlete volunteers aged 18 to 25 years recruited at our university. Exclusion criteria included (1) receiving any treatment or prescribed drugs from a medical doctor, (2) suffering from severe cardiovascular disorder, liver dysfunction, renal dysfunction, respiratory disorder, endocrine disorder, metabolic disorder, or a history of these disorders, (3) possible allergies related to the test food, or (4) participating or having participated in other clinical trials that might affect glucose metabolism within the past 3 months. All participants received an explanation about the purpose, methods, expected results, and method of outcome review; as well as the protection of personal information, potential benefits, and disadvantages of participating in the trial. Participants were told that participation was at their own free will, and that they could withdraw at any time. All participants provided written, informed consent to participate in the trial. The protocol was designed according to the Declaration of Helsinki and ICH E9 statistical principles for clinical trials (Iyaku-Shin-Dai 1047, Ministry of Health of Japan), and was approved by the Ethics Committee of Juntendo University Graduate School of Sports and Health Sciences (Approval #28-67). The study protocol was registered on the University Hospital Medical Information Network – Clinical Trials Registry (UMIN-CTR ID: UMIN000023726).

**Study Design**

A randomized, double-blind, placebo-controlled, crossover trial was conducted. Participants visited the laboratory at 08:30 after an overnight fast, having finished their dinner by 21:00 the day before the test and consuming only water after dinner. After measuring baseline FBG levels, participants consumed the test food (3 hard capsules of either pinitol 600 mg/capsule or placebo [dextrin]) (Table 3) and then ate breakfast (577 kcal; protein 14.0 g; fat 5.6 g; and carbohydrate 117.7 g). The breakfast used was a big size Udon noodle with grated daikon radish “Ohmori Bukkake Oroshi Udon” which was a product of Seven-Eleven Japan (Tokyo, Japan). Test food was prepared by Nihon Advanced Agri Co., Ltd (Shiga, Japan) using their pinitol. The appearance, weight, smell and taste of the pinitol and placebo were confirmed; that is, the participants and the investigators were blinded to the assignment. Blood glucose concentrations were measured immediately (0) and 30, 60, 90, and 120 minutes after breakfast using a portable glucose meter (Nipro Care Fast C, Nipro, Tokyo, Japan). iAUC[120] were calculated using Simpson’s rule; areas below baseline were ignored. Participants completed the protocol twice in a crossover

| Ingredient                  | Pinitol | Placebo |
|-----------------------------|---------|---------|
| Ice plant powder, mg        | 25      | 0       |
| Pinitol, mg                 | 600     | 0       |
| Zinc fortified yeast, mg^2  | 50      | 50      |
| Manganese fortified yeast, mg^2 | 40    | 40      |
| Vitamin C, mg               | 100     | 100     |
| Vitamin B1, mg              | 10      | 10      |
| Vitamin B2, mg              | 5       | 5       |
| Vitamin B6, mg              | 5       | 5       |
| Niacin, mg                  | 5       | 5       |
| Panthenic acid, mg          | 5       | 5       |
| Folic acid, µg              | 100     | 100     |
| Vitamin B12, µg             | 50      | 50      |
| Cellulose, mg               | 440     | 440     |
| Dextrin, mg                 | -       | 625     |
| Silica gel, mg              | 9       | 9       |
| Calcium stearate, mg        | 26      | 26      |
| Total, mg                   | 1320    | 1320    |

^50 mg contained 5 mg of zinc.
^40 mg contained 4 mg of manganese.
fashion, with a wash-out period of 1 day or more between sessions. The order of the test food was randomized.

**Statistical Analysis**

The iAUC_{120} of pinitol and placebo was compared using the generalized estimating equation (GEE): the model included the subject identification (ID) as a subject variable, test food (pinitol/placebo), and the test day as within-subject variables, and the interaction (test food × test day). Blood glucose kinetics in participants in IGT group were also analyzed by GEE: the model included subject ID as a subject variable, test food (pinitol/placebo), measuring point (baseline and 0, 30, 60, 90, and 120 minutes after breakfast), and the test day as within-subject variables, and all pairs of within-subject variables as interactions. The estimated marginal means at the same time point were compared between pinitol and placebo with a *P*-value adjusted by sequential Sidak procedure. SPSS ver. 19 (Japan IBM, Tokyo, Japan) was used for the analyses. Statistical significance was set at *P* < 0.05.

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The authors declared no potential conflicts of interest with respect to the research, authorship, and publication of this article.

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