



Technical Literature

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PI2 Lowers Glycemic Load

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Key Conclusions

- **Human studies suggest that reducing glycemia is an effective means to reduce and maintain weight.**
- **Schwartz et al. and Spreadbury et al. have shown that ingesting PI2 lowers the glycemic load.**
- **These studies showed that PI2 was equally effective in either liquid or encapsulated form supplements when taken prior to a meal.**

Introduction

It is estimated by the National Institutes of Health that two-thirds of people in the United States are overweight or obese (19). The definition of obesity varies, but in general it is a chronic condition defined by excess body fat. Obesity results from insufficient caloric expenditure (through exercise and physical activity) and excessive caloric intake. Certain people have a genetic predisposition to obesity; however, environment and lifestyle influence overeating and the lack of physical activity to a greater extent than genetics.

The obesity epidemic in the U.S. closely corresponds to an increase in the consumption of diets with a high glycemic load (simple carbohydrates such as sugars, white bread, desserts, soft drinks, beer, wine, cereals, etc.). The role of simple carbohydrates in weight gain and obesity is not completely clear; however, evidence increasingly suggests that they are closely related (3, 7, 9, 14). Consumption of both simple and complex carbohydrates (pasta, brown rice, grains, vegetables, raw fruits, etc.) raises blood glucose levels, which in turn stimulates insulin release by the pancreas. Simple carbohydrates are more rapidly absorbed into the blood stream than complex carbohydrates causing hyperglycemia (elevated blood glucose) and hypersecretion of insulin. Elevated insulin levels promote the growth of fat tissue and can cause weight gain. Additionally, hypersecretion of insulin leads to a rapid drop in blood glucose level, prompt onset of hunger, and the desire to eat soon after the initial meal. This cycle leads to more frequent meals, overall increase in caloric intake, and obesity (8,15).

Recent studies indicate that the risks of diseases such as type 2 diabetes and coronary heart disease are strongly related to the carbohydrate content of the overall diet (3, 14). These studies indicate that chronic hyperglycemia can lead to increased fat production and accumulation, and may contribute significantly to the development of obesity and other chronic obesity-related diseases (3, 14). In addition, long-term animal models have also shown that diets high in simple carbohydrates promote weight gain, visceral fat stores, and higher concentrations of lipogenic enzymes than do moderate calorie, macronutrient controlled, complex carbohydrate diets (3). Moreover, studies have shown that diets based on low-fat foods that produce a low glycemic response may enhance weight

control in the overweight and obese because they promote satiety, maintain insulin sensitivity, and minimize postprandial insulin secretion (3, 17, 21).

Postprandial blood glucose levels are influenced by the rate of gastric emptying (11). Reducing the rate at which carbohydrates are digested and thus delaying glucose absorption may aid in reducing hyperglycemia. Therefore, controlling gastric emptying by dietary and pharmacological means in order to minimize postprandial glucose represents a new approach to glycemic control. Following consumption of a meal, cholecystokinin (CCK), a well-characterized gut peptide hormone, is secreted into the bloodstream by endocrine cells (5, 12, 13). This hormone then acts on various tissues including the gastrointestinal tract, where it stimulates enzyme secretion and delays gastric emptying, creating a feeling of fullness (1). CCK also acts on the brain leading to feelings of satiety (5).

Proteinase inhibitors (PI2), a mixture of naturally occurring proteins found in white potatoes and the active ingredient of Slendesta™ Potato Protein Extract, has been shown to enhance the release of CCK (4). Oral administration of PI2 has been documented to increase CCK levels, reduce hunger, delay gastric emptying, and decrease energy intake in humans (9, 10, 13, 14). This report describes two recent research investigations aimed at determining the effect of oral administration of PI2 on glycemic load in humans.

Effect of PI2 on postprandial biomarkers in type 2 diabetics

In 1994, Schwartz et al. performed a series of studies to determine whether oral administration of PI2 would delay gastric emptying and modulate postprandial glucose levels in recently diagnosed (within three years) type 2 diabetic patients (16). Six type 2 diabetic patients participated in the study and each served as their own control. Each subject came for two visits, separated by at least one week; during one visit the patients consumed a glucose/protein solution, while the patients consumed the same glucose/protein solution with the addition of 1.5 g PI2 during the other visit. During each of the studies the rate of gastric emptying was examined. Several biological markers such as serum insulin, plasma CCK, plasma glucose, and plasma gastric inhibitory polypeptide (GIP) were also assessed, both pre- and postprandially.

One of the test subjects required insulin treatment and therefore responded irregularly with respect to postprandial glucose and insulin levels. Therefore, data analysis did not include this individual, although statistical comparison with and without this individual resulted in the same outcome. With the exception of the above subject, all individuals showed a decrease in plasma glucose levels when PI2 was administered (**Figure 1**). Decreased plasma glucose levels also correlated well with reduced GIP levels, which are a reliable indicator of glucose absorption in the small bowel. Plasma insulin levels in all but the test subject using insulin significantly decreased upon addition of PI2 to the ingested meal. Statistically significant differences were seen at 60 and 105 minutes postprandial. Plasma CCK levels were found to have significantly increased only at 15 minutes post-ingestion. The rate of post-ingestion gastric emptying was also monitored for two hours. The researchers found that nearly every test subject (5 out of 6) experienced a substantial increase in retention of the meal containing PI2.

Effect of PI2 on postprandial plasma glucose in normal subjects

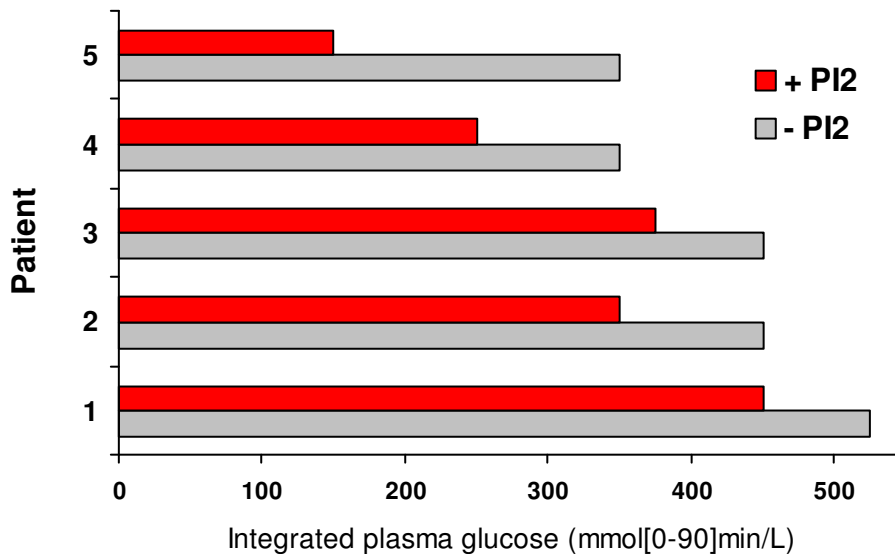


Figure 1. Individual variations in integrated area under the curve for postprandial glucose (0-90 minutes) with and without addition of PI2 to the meal (16).

In 2003, a study was undertaken by Spreadbury et al. to examine the effect of PI2 on postprandial plasma glucose levels (18). The Spreadbury trial was a randomized, placebo-controlled, double-blind study involving 39 healthy test subjects. As in the Schwartz study, test subjects served as their own control. Test subjects were administered two of three different dosages of PI2 (7.5, 15, or 30 mg) in an encapsulated form 30 minutes prior to meal ingestion. The participants also consumed a traditional mixed meal, not a liquid meal as in the Schwartz study.

Plasma glucose levels were determined for each test subject 30 minutes prior to and every 30 minutes, up to 120 minutes, after the meal challenge. One of the test subjects declined to provide blood samples and was therefore removed from the statistical analysis with respect to postprandial glucose levels. ANOVA analysis showed a statistically relevant effect on postprandial blood glucose with PI2 treatment. A significant difference in postprandial blood glucose was observed in subjects treated with the 15 and 30 mg doses ($p < 0.05$), with no significant difference in response between the two treatment doses; however, participants treated with 7.5 mg showed no significant decline in postprandial blood glucose compared to placebo. The overall decrease in blood glucose compared to placebo was 25% and 20%, respectively, for the 15 and 30 mg doses. The integrated area under the blood-glucose time curve for the 15 and 30 mg doses were 29.5% and 24.5%, respectively, compared to placebo (**Figure 2**).

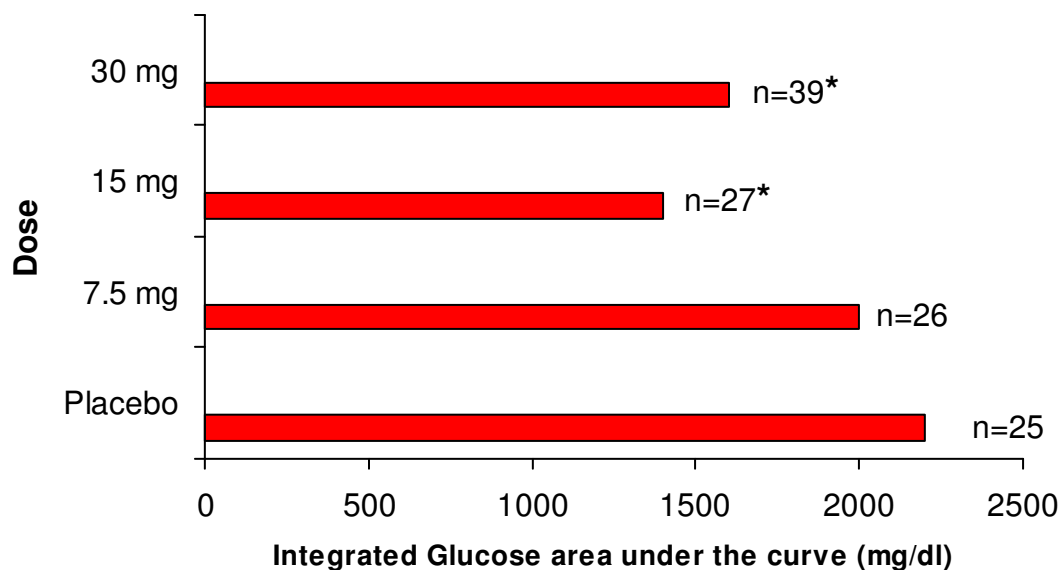


Figure 2. Postprandial effect of increasing dose integrated under the blood glucose curve after a test meal. Subjects ingested placebo, 7.5, 15, or 30 mg PI2 30 minutes prior to a standardized test meal. Blood sugar was measured at time 0 (pre-meal), and at 30, 60, 90, and 120 minutes post-meal. All subjects received placebo, and were randomly assigned two of the three other doses. * $p < 0.05$ vs. placebo (18).

Conclusions

The rise in obesity rates has been accompanied by high glycemic diets resulting in chronic glycemia and hypersecretion of insulin (5, 26). This, in turn, results in decreased fat breakdown, increased fat accumulation, faster onset of hunger, and subsequent food intake (9, 14). This may not only contribute to obesity, but other chronic diseases, including diabetes and cardiovascular disease (14). Weight loss studies in humans suggest that reducing the glycemia experienced by the body is an effective means to reduce and maintain weight (17, 21). Subjects consuming isocaloric diets consisting of low glycemic index foods lose more weight or maintain their weight relative to those consuming high glycemic index foods (17, 20, 21).

PI2, the active component of Slendesta Potato Protein Extract, is proposed to exert its effect on postprandial glucose by enhancing the release of CCK (5). Previous studies demonstrated that large doses of purified PI2 enhance the release of CCK and decrease energy intake in humans (8, 15). The results presented in Schwartz et al. are consistent with these findings since they also show increased CCK release upon PI2 administration (16). Additionally, these results show that administration of PI2 can delay gastric emptying time and decrease postprandial serum insulin levels (16). Together Schwartz et al. and Spreadbury et al. have shown that ingesting PI2 lowers the glycemic load (16, 18). In both studies consumption of various dosages of PI2 resulted in decreased postprandial blood glucose levels after a meal challenge. In Spreadbury et al. the dose of PI2 was reduced 100-fold, as compared to Schwartz et al., but its effects on postprandial blood glucose were maintained using these lower doses, indicating that the effective dose of PI2 likely lies between 7.5 and 15 mg. In addition, together these studies showed that PI2 was equally efficacious in either a liquid form taken with a meal or as an encapsulated supplement taken prior to a meal. Combined, these reported results indicate that PI2 supplied by Slendesta lowers the glycemic load after a meal, which is recognized in the literature as a critical factor for weight management.

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