

Effects of a palatinose-based liquid diet (Inslow) on glycemic control and the second-meal effect in healthy men

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Abstract

Postprandial hyperglycemia induces prolonged hyperinsulinemia, which is a risk factor for type 2 diabetes mellitus. Foods with a low glycemic index blunt the rapid rise in postprandial plasma glucose and insulin levels. We herein investigated the effects of a novel, palatinose-based liquid diet (Inslow, Meiji Dairy Products, Tokyo, Japan) on postprandial plasma glucose and insulin levels and on the rate of substrate oxidation in 7 healthy men. Furthermore, to examine the effects of Inslow on the second-meal effect, we quantified our subjects' postprandial plasma glucose, insulin, and free fatty acid levels for up to 7 hours after they ingested a breakfast containing Inslow or control formula, followed by a standard lunch 5 hours later. Our results showed that peak plasma glucose and insulin levels 30 minutes after Inslow loading were lower than after control formula loading. Postprandial fat oxidation rates in the Inslow group were higher than in the control formula group ($P < .05$). In the second-meal effect study, plasma glucose and insulin levels after lunch in the Inslow group were lower than in the control formula group ($P < .01$), although the peak levels in these groups were not different. The free fatty acid concentration in the Inslow group immediately before lunch was significantly lower than in the control formula group ($P < .05$). In conclusion, consumption of Inslow at breakfast appears to improve patient glycemic control by reducing their postprandial plasma glucose and insulin levels after lunch (second-meal effect).

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1. Introduction

Postprandial hyperglycemia, found in patients with prediabetes, is a reflection of reduced insulin sensitivity, reduced insulin secretory capacity, and/or excessive energy expenditure. In the latter case, hyperglycemia leads to increased secretion of late-phase insulin, thereby promoting the accumulation of fat and reduction in fat oxidation, and in the development of insulin resistance. Thus, it is theorized that diabetes may be preventable by inhibiting this postprandial hyperglycemia. Postprandial plasma glucose levels are influenced by both the amount and the type of carbohydrates in food. The glycemic index (GI),

originally described by Jenkins et al [1], is a ranking of carbohydrates based on their immediate effects on blood glucose levels. Several studies recently reported that low-GI diets improved both glycemic control and blood lipid profiles in diabetic patients and healthy subjects [2,3]. Furthermore, it has also been shown that children with type 1 diabetes mellitus who were on a low-GI diet maintained better hemoglobin A_{1c} concentrations long term [4]. Glycemic index values vary depending on how foods that contain carbohydrates are cooked and on the types of carbohydrates and fiber they contain.

Isomaltulose (palatinose), a sucrose isomer found in honey [5], was found to be metabolized by isomaltase, and less rapidly, although completely, cleaved in the intestine than sucrose [6]. Ingestion of palatinose by type 2 diabetic humans and rats resulted in a reduction in their postprandial plasma glucose and insulin levels [7,8]. Inslow (Meiji

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Dairy Products) is a recently developed liquid formula that contains palatinose. In our previous study, long-term ingestion of this balanced formula suppressed postprandial hyperglycemia and fat accumulation in adipose tissue, and improved insulin sensitivity in rats [9].

Several studies suggested that consumption of a low-GI breakfast might improve glucose tolerance after lunch; this improvement has been referred to as the second-meal effect [10,11]. Clearly, it is in the interest of disease prevention and treatment that the mechanism of this effect be examined. The objective of this study was to investigate the effects of Inslow ingestion at breakfast on postprandial plasma glucose, substrate oxidation, and the second-meal effect in healthy men.

2. Methods

2.1. Subjects

Seven healthy male subjects with a stable body weight participated in this study. Their mean \pm SEM age and body mass index were 31.6 ± 0.5 years and 23.0 ± 1.0 kg/m², respectively. All subjects gave their informed consent to participate in this study, and the study protocol was approved by the human subjects ethical committee of the Tokushima University Hospital (Tokushima, Japan) and conducted in accordance with the Helsinki Declaration.

2.2. Liquid formula and test meal

Inslow was prepared by partially replacing dextrin in control formula with 55.7% palatinose. Its final constituents, listed in Table 1, included palatinose, dextrin, xylitol, dietary fiber, and mixed carbohydrates; its final protein, fat, and carbohydrate concentrations were 20.0%, 29.7%, and 50.3%, respectively. The control formula was a dextrin-based enteral liquid formula that also contained sucrose; its protein, fat, and carbohydrate concentrations were 14.0%, 31.0%, and 55.0%, respectively (Table 1). On the night before testing, all subjects ate the same dinner, which included boiled rice, sautéed beef and vegetables, mixed salad, miso soup, and kiwi fruit; this meal provided 14.5% energy from protein, 24.2% from fat, and 61.3% from carbohydrate, and had a total energy content of 2743 kJ (Table 2). The breakfast foods and lunch diets that were used in the second-meal experiment contained the following protein, fat, and carbohydrate levels, respectively: 14.2% and 14.3%, 23.8% and 22.8%, and 62.0% and 62.9%; their respective energy contents were 1139.7 and 3092 kJ (Table 2).

Table 1
Product composition

	Inslow	Control formula
Energy (kJ/mL)	4.18	4.18
Protein (% of energy)	20.0	14.0
Fat (% of energy)	29.7	31.0
Carbohydrate (% of energy)	50.3	55.0
Main carbohydrate composition	Palatinose (55.7%)	Dextrin (97.2%)

Table 2
Energy composition of the test meals

	Dinner	Breakfast	Lunch
	Test meal	Test meal + formula	Test meal
Energy (kJ)	2743.0	1139.7 + 1046.0	3092.4
Protein (% of energy)	14.5	15.0	14.3
Fat (% of energy)	24.2	24.6	23.0
Carbohydrate (% of energy)	61.3	60.4	62.7

The formula is Inslow or control formula whose composition is shown in Table 1.

2.3. Experimental design

2.3.1. Formula loading and substrate oxidation experiment

Two randomized crossover studies with a washout period of 2 weeks were conducted in 7 subjects. On the day before their first test, subjects ate a balanced standard dinner (see above); however, no food or drink (except water) was allowed after 9:00 PM, nor were they permitted to exercise after that time. Liquid formula loading (500 mL; 2092 kJ) tests (Inslow or control formula) were conducted on separate days at 2-week intervals; subjects completely consumed one liquid formula within 10 minutes. Peripheral blood samples were collected at times 0, 30, 60, 120, 180, and 240 minutes, and plasma glucose, insulin, and free fatty acid (FFA) levels were measured. At these same time points, energy expenditure and substrate oxidation rates were determined from the subjects' respiratory gas exchange measurements. An automatic, computerized indirect calorimeter (Aero monitor AE 300, Minato Medical Science, Tokyo, Japan) was used to determine oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$). Measurements of resting energy expenditure were taken over the course of 30 minutes before fasting blood samples were collected (baseline). During the course of these measurements, continuous ventilatory volumes ($\dot{V}O_2$ and $\dot{V}CO_2$) were displayed on a computer screen at 15-second intervals, and mean minute-by-minute values were recorded. The liquid formulas were consumed within 10 minutes, after which the subjects' postprandial $\dot{V}O_2$ and $\dot{V}CO_2$ were measured over 10 minutes every 30 to 240 minutes. The subjects' nonprotein respiratory quotient was determined from their $\dot{V}O_2$ and $\dot{V}CO_2$ described by Nagai et al [12]. Energy expenditure, and carbohydrate and fat oxidation rates were calculated using the tables of Lusk [13]. During the course of sample acquisition, the subjects read a book and rested quietly. Two weeks later, the above routine was repeated.

2.3.2. Second-meal experiment

During the 12 hours before the initiation of the second part of this study, our 7 subjects ate the same dinner described above. No food or drink (except water) was allowed after 9:00 PM, nor was exercise permitted after that time. At 7:00 AM the following morning, the subjects ingested a 2186-kJ breakfast containing 1139.7 kJ of a test meal (sandwiches and orange fruit) plus either 1046 kJ of Inslow or 1046 kJ of control formula. Blood samples, in addition to

baseline, were then collected at 30, 60, 120, 180, and 300 minutes. Blood samples were also collected before and 30, 60, and 120 minutes after the subjects ate a standard, 3092-kJ lunch that consisted of boiled rice, hamburger, boiled vegetables, mixed salad, miso soup, and fruit yogurt; the subjects consumed their lunch from 12:00 to 12:20 PM. Two weeks later, the above routine was repeated.

2.4. Analytic method

Plasma samples were separated and kept at -20°C until use. Plasma glucose was measured using the glucose oxidase method. Plasma insulin levels were measured by radioimmunoassay using a commercially available kit (EIKEN, Tokyo, Japan). Plasma FFA levels were measured enzymatically using a commercially available kit (WAKO, Osaka, Japan). The total incremental area under the curve (AUC) for plasma glucose and insulin, as well as carbohydrate and fat oxidation rates were calculated for a 240-minute period after each test meal.

2.5. Statistical analyses

Data are presented as means \pm SEM. Significant differences between groups were calculated using the paired Student *t* test. All statistical analyses were performed using StatView software (version 5.0-J for Windows, SAS Institute, Cary, NC).

3. Results

3.1. Postprandial changes in plasma glucose and insulin levels and nutrient oxidation during Inslow or control formula loading

Postprandial plasma glucose and insulin levels and nutrient substrate oxidation rates during Inslow or control

formula loading are shown in Fig. 1. Peak plasma glucose and insulin levels were observed at 30 minutes during both loading tests (plasma glucose: 5.7 ± 0.2 and 6.5 ± 0.4 mmol/L, respectively, $P < .01$; insulin: 297.9 ± 31.2 and 415.2 ± 48.4 pmol/L, respectively, $P < .01$). Furthermore, postprandial plasma glucose levels at 60 minutes (4.6 ± 0.2 and 5.4 ± 0.2 mmol/L, respectively, $P < .05$) and insulin levels at 60 minutes (190.9 ± 44.6 and 306.6 ± 50.0 pmol/L, respectively, $P < .05$) and 120 minutes (80.3 ± 9.8 and 134.4 ± 18.7 pmol/L, respectively, $P < .05$) after Inslow loading were significantly lower than those after control formula loading. The AUC from time 0 through 120 minutes for both plasma glucose and insulin levels during Inslow and control formula loading are shown in Fig. 2. The plasma glucose incremental AUC after Inslow loading was significantly lower than for control formula loading (Inslow, 35.1 ± 4.3 mmol $\text{min}^{-1} \text{L}^{-1}$; control formula, 77.9 ± 13.3 mmol $\text{min}^{-1} \text{L}^{-1}$; $P < .05$). The postprandial insulin AUC in the Inslow group was markedly reduced compared with that in the control formula group (Inslow, 20229 ± 3145 pmol $\text{min}^{-1} \text{L}^{-1}$; control formula, 31927 ± 4008 pmol $\text{min}^{-1} \text{L}^{-1}$; $P < .01$). The insulinogenic index [Δ insulin ($\mu\text{U}/\text{mL}$)/ Δ plasma glucose (mg/dL)], a measure of early insulin secretion, in the Inslow group at 30 minutes was significantly higher than in the control formula group (3.2 ± 0.6 vs 2.5 ± 0.5 , respectively, $P < .05$). Free fatty acid levels fell somewhat after 60 minutes in the Inslow group, but then slowly rose relative to baseline until 240 minutes. On the other hand, FFA levels in the control formula group rapidly fell through 60 minutes ($P < .01$), after which they quickly recovered and increased until 240 minutes.

Our subjects' fasting and postprandial energy expenditure, as well as carbohydrate and fat oxidation are shown

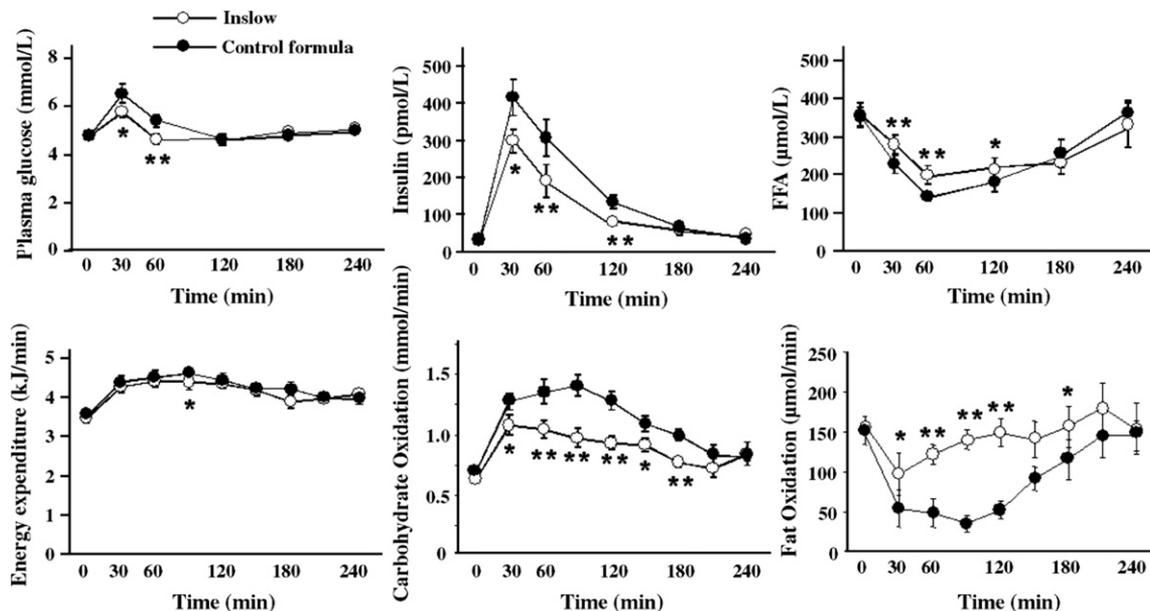


Fig. 1. Changes in plasma glucose, insulin, and FFA levels, as well as energy expenditure and substrate oxidation after Inslow and control formula loading. Values are mean \pm SEM. * $P < .05$ and ** $P < .01$ vs control formula loading (paired *t* test).

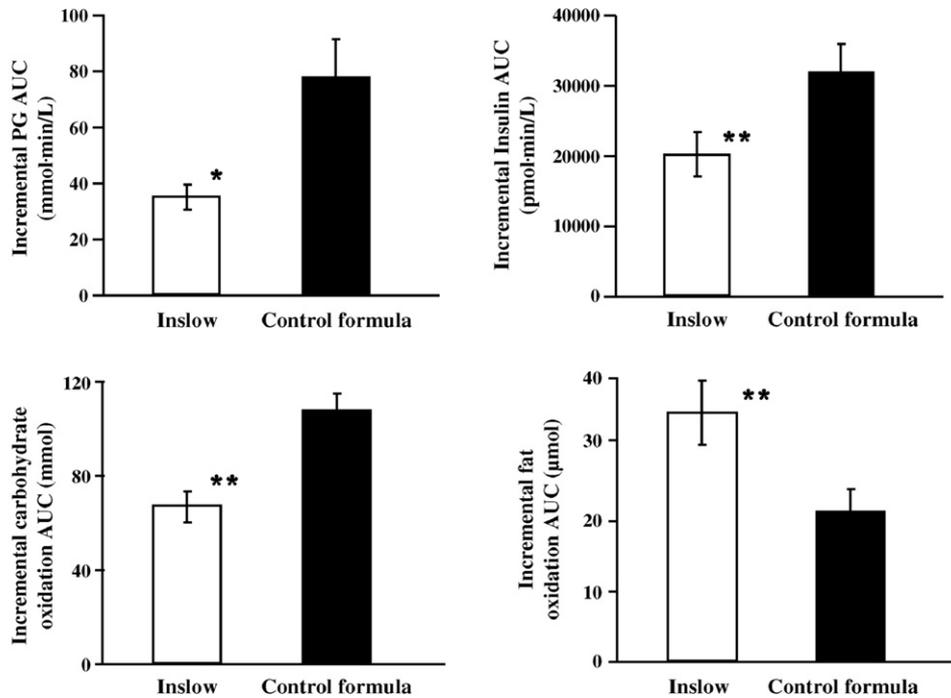


Fig. 2. Incremental AUCs for plasma glucose (PG), insulin, carbohydrate oxidation, and fat oxidation after Inslow and control formula loading. Values are means \pm SEM. * $P < .05$ and ** $P < .01$ vs control formula loading (paired t test).

in Fig. 1. Results showed that there was a gentle rise in energy expenditure in both the Inslow and control formula groups. Postprandial carbohydrate oxidation from 30 to 180 minutes after Inslow loading was lower than after control formula loading. There were also significant differences in total incremental carbohydrate oxidation over 240 minutes in the Inslow and control formula loading groups (Inslow, 66.8 ± 9.1 mmol; control formula, 107.6 ± 10.2 mmol; $P < .01$). In contrast, fat oxidation rates from 30 to 180 minutes were significantly higher in the Inslow group. Finally, total incremental fat oxidation over the course of 240 minutes was higher in the Inslow group (34.2 ± 4.4 μ mol [Inslow] vs 20.6 ± 3.2 μ mol [control formula], $P < .01$).

3.2. Effects of Inslow or control formula at breakfast on plasma glucose, insulin, and FFA levels before and after a standard lunch

We investigated whether Inslow ingestion at breakfast may improve glucose tolerance after lunch, referred to as the second-meal effect. Changes in serum plasma glucose, insulin, and FFA levels after Inslow loading at breakfast were similar to those in the formula loading experiment as shown in Fig. 1 (Fig. 3). Interestingly, plasma glucose levels 60 minutes after lunch were significantly reduced in the Inslow compared with those in the control formula group (7.0 ± 0.2 and 7.9 ± 0.4 mmol/L, respectively, $P < .05$). The foregoing notwithstanding, peak plasma glucose levels were not different between groups. Furthermore, insulin levels 120 minutes after lunch in the Inslow group were markedly reduced compared with those in the control

formula group (Inslow, 152.4 ± 21.1 pmol/L; control formula, 218.9 ± 28.2 pmol/L; $P < .05$).

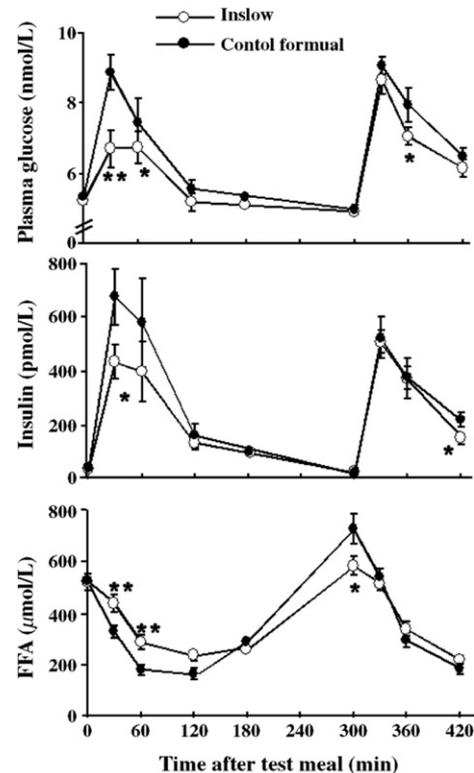


Fig. 3. Plasma glucose, insulin, and FFA levels after an Inslow or control formula breakfast, followed by a standard lunch. Values are means \pm SEM. * $P < .05$ and ** $P < .01$ vs control formula loading (paired t test).

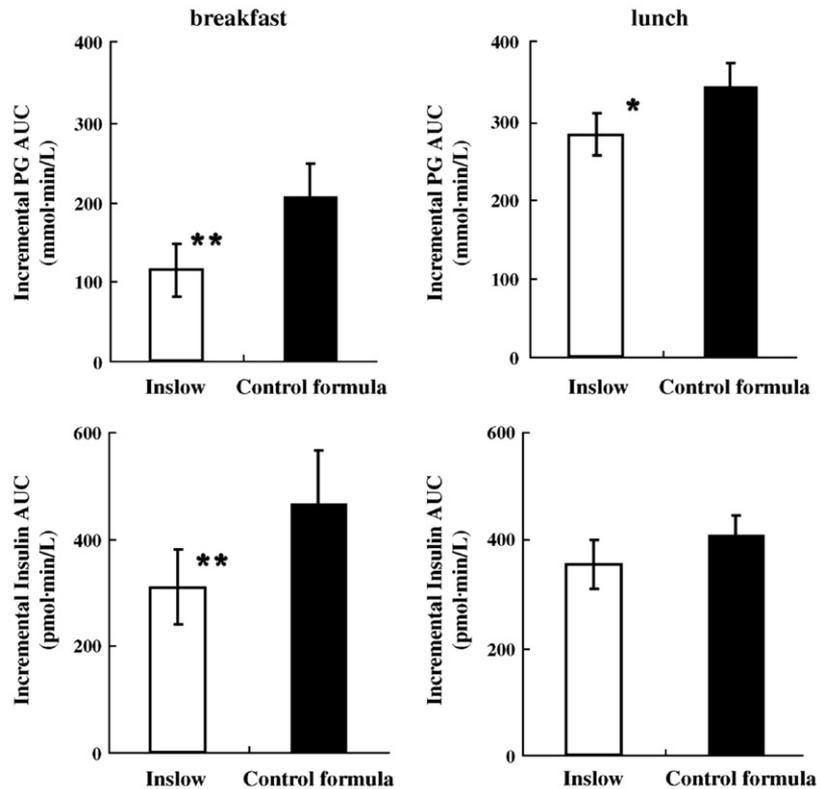


Fig. 4. Plasma glucose (PG) and insulin AUC values after an Inslow or control formula breakfast, followed by a standard lunch (breakfast, 0-120 minutes; lunch, 300-420 minutes). Values are means \pm SEM. * $P < .05$ and ** $P < .01$ vs control formula loading (paired t test).

Plasma FFA concentrations after breakfast in the Inslow group fell more slowly than in the control formula group. The lowest FFA levels were found at 120 minutes; values in the Inslow and control formula groups were 237.0 ± 18.7 and 169.0 ± 21.4 $\mu\text{mol/L}$, respectively. Interestingly, FFA levels before lunch in the Inslow group were significantly lower than in the control formula group (Inslow, 564.1 ± 36.8 $\mu\text{mol/L}$; control formula, 706.1 ± 50.3 $\mu\text{mol/L}$; $P < .01$), although levels were similar after lunch.

The incremental plasma glucose and insulin AUCs during breakfast (0-120 minutes) and lunch (300-420 minutes) in both groups are shown in Fig. 4. The AUC for plasma glucose in the Inslow group after both breakfast and lunch was significantly lower than in the control formula group (breakfast Inslow, 115.0 ± 33.8 $\text{mmol min}^{-1} \text{L}^{-1}$; control formula, 208.1 ± 40.5 $\text{mmol min}^{-1} \text{L}^{-1}$, $P < .01$; lunch Inslow, 283.2 ± 26.9 $\text{mmol min}^{-1} \text{L}^{-1}$; control formula, 344.0 ± 30.4 $\text{mmol min}^{-1} \text{L}^{-1}$, $P < .05$). The AUC for insulin in the Inslow group at breakfast was also significantly lower than in the control formula group (Inslow, 3111 ± 701 $\text{pmol min}^{-1} \text{L}^{-1}$; control formula, 4680 ± 993 $\text{pmol min}^{-1} \text{L}^{-1}$, $P < .01$), whereas the AUC in the Inslow group at lunch showed a tendency toward lower values compared with that in controls (Inslow, 3554 ± 449 $\text{pmol min}^{-1} \text{L}^{-1}$; control formula, 4020 ± 353 $\text{pmol min}^{-1} \text{L}^{-1}$; $P < .08$).

4. Discussion

This is the first human study that was designed to evaluate the effects of Inslow on plasma glucose and insulin concentrations in healthy subjects. Previous studies suggested that nutrients with a low GI but not total carbohydrate content could decrease the risk of developing type 2 diabetes mellitus [14,15]. Important considerations regarding the development of a dietary regimen that might help prevent type 2 diabetes mellitus include the types of fats and carbohydrates that it contains, as well as the subject's total energy intake [16,17]. Several studies suggested that high-sucrose and high-fructose diets induce hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and insulin resistance [18-21]. Inslow was clearly beneficial in preventing an excessive postprandial rise in plasma glucose and insulin levels. Palatinose, the primary carbohydrate constituent in Inslow, is metabolized to glucose and fructose by intestinal isomaltase at a rate that is one fourth that of sucrose, although completely cleaved [22]. In our previous study, long-term use of Inslow suppressed hyperinsulinemia and fat accumulation in adipose tissue, and improved insulin sensitivity in rats [9]. Thus, collectively, our data suggest that palatinose use does not induce insulin resistance and may be a useful addition to carbohydrate meals to lower their GI.

The question remains as to whether the beneficial effects of the Inslow diet were due to the presence of palatinose and/

or to differences in the protein/carbohydrate ratio between the 2 diets. Protein intake is known to stimulate insulin release [23,24]. Thus, the fact that the amount of milk protein in Inslow was higher than that in the control formula could have accounted for the enhanced insulin response and reduced postprandial glucose levels in the subjects that consumed it. Although Van Loon et al [25] reported that the ingestion of carbohydrates in combination with insulinotropic amino acids such as arginine and leucine resulted in an enhanced insulin response, whey and casein (milk protein) were not found to significantly affect carbohydrate-induced insulin secretion. Thus, it seems reasonable to conclude that the above benefits of Inslow ingestion were primarily due to the presence of palatinose in the formulation.

Postprandial fat oxidation was 50% higher after Inslow loading than after control formula loading. The assumption is that a high-GI diet significantly increases serum insulin and glucose levels, thereby promoting carbohydrate oxidation and suppressing fat oxidation. However, carbohydrate and fat oxidation was reported to be similar after ingestion of either a high- or a low-GI meal, although the insulin response after the low-GI diet was lower [26]. It is of interest that substrate oxidation varies depending on the amounts and types of carbohydrates, lipids, and proteins ingested. Ingestion of a high-protein meal (30%) resulted in higher postprandial fat oxidation rates compared with controls (15%) in both obese and lean subjects [27]. It has been suggested that the enhanced oxidation of fat that occurs after ingestion of a high-protein diet could be directly due to the reduction in carbohydrate intake (15% in that diet). The protein content of the Inslow diet differs by only 5% from that in the control formula diet, whereas postprandial fat oxidation rates in the Inslow group were twice that of the control group. Postprandial fat oxidation rates were reported to increase after the ingestion of olive oil [28], fish oil [29], and resistant starch [30]. In our study, the ingestion of palatinose together with oleic acid as the primary fat source in the Inslow diet may have had the added benefit of slowing fat and carbohydrate absorption while increasing the oxidation of fat. The fact that Inslow significantly increased postprandial fat oxidation suggests that it might be beneficial in limiting fat accumulation long term. In support of these findings, our previous study in rats showed that Inslow suppressed the accumulation of fat in adipose tissue in addition to improving insulin sensitivity [9]. These data suggest that Inslow might be useful in preventing obesity and metabolic syndrome.

Slowing of the absorption and digestion of breakfast starch was reported to improve glucose tolerance at lunch [10,11]. It is conceivable that FFAs participate in this second-meal effect. Ingestion of a small (compared with large) amount of carbohydrates at breakfast was shown to result in a more elevated postprandial FFA response and impaired glucose tolerance after lunch [31,32]. Furthermore, a high-carbohydrate/low-GI diet was reportedly effective in suppressing FFAs and improving carbohydrate tolerance after a second meal [31,33]. It is interesting that this rapid elevation in FFAs

before lunch could be suppressed by the consumption of Inslow for breakfast. High levels of plasma FFAs may contribute to insulin resistance, increased hepatic glucose production [34,35], and reduced glucose utilization [36,37]. Only a small increase in plasma insulin is required to inhibit hormone-sensitive lipase and reduce FFA release from adipose tissue [38]. Sustained elevations in plasma FFA concentrations were reported to be associated with an increased risk of developing type 2 diabetes mellitus [39], possibly due to their reduction in insulin secretion [40,41] and action [37]. Suppression of postprandial plasma FFAs levels with its associated insulin-sparing effects may contribute to the prevention of impaired glucose tolerance and metabolic syndrome.

Several epidemiologic studies found that increasing whole-grain intake was inversely associated with metabolic syndrome and mortality [42,43]. Although a whole-grain diet has a low GI, whole-grain intake suppressed insulin levels [44] but not fasting glucose and glycated hemoglobin levels [42]. It is particularly noteworthy that Inslow suppressed both hyperglycemia and hyperinsulinemia.

The importance of breakfast carbohydrate tolerance was noted in studies in which this meal was the second meal that followed ingestion of a low-GI dinner [45,46]. A more recent study demonstrated that the omission of breakfast impaired postprandial insulin sensitivity [47]. These data highlight the second-meal benefits of ingesting a low-GI breakfast vis-à-vis the improvement of insulin sensitivity as well as glucose and fat metabolism.

In conclusion, the consumption of Inslow at breakfast reduced postprandial plasma glucose and insulin levels after lunch, that is, the second-meal effect. Inslow might be useful in maintaining glycemic control and reducing complications in individuals with diabetes.

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