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Attenuating Effect of Isomaltodextrin Contained in Bread on Postprandial Plasma Glucose Levels in Healthy Humans:

A Randomized, Placebo-controlled, Double-blind Crossover Study

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● **Abstract**

Objective: The purpose of this study was to examine whether isomaltodextrin (IMD) attenuates elevated blood glucose levels following meal intake.

Methods: Overnight-fasted subjects (n = 30) consumed bread (containing IMD or not containing IMD) with breakfast, and blood glucose levels were determined over time from immediately before to 120 minutes after meal intake. The study was conducted with or without intake of 2.93 g of IMD in a double-blind crossover study.

Results: No differences were observed in blood glucose levels over time after the meal between IMD intake and non-IMD intake in all subjects. However, a stratified analysis of subjects with a tendency for increased postprandial blood glucose levels showed a significant higher attenuating effect of IMD intake on blood glucose elevation compared with non-IMD intake in terms of blood glucose levels over time and area under the curve.

Conclusion: Results of this study suggest that IMD attenuates elevated blood glucose levels following meal intake.

Key Words: Isomaltodextrin, Soluble dietary fiber, Postprandial blood glucose level, Bread

1. INTRODUCTION

Excessively high blood glucose levels following a meal is a risk factor for type 2 diabetes mellitus[1]. In 2013, the number of patients with diabetes aged 20–79 years was estimated at approximately 7.2 million in Japan and approximately 380 million worldwide, according to a report by the International Diabetes Federation[2]. In most developed countries, uncontrolled diabetes is associated with complications such as diabetic neuropathy, renal failure, blindness, large vessel disease, and death[1]. Therefore, it is extremely important to control excessive changes in blood glucose levels following food intake.

Isomaltodextrin (IMD) is a new highly branched α-glucan produced enzymatically from starch using α-glucosyltransferase and α-amylase derived from *Paenibacillus alginolyticus* PP710[3]. IMD is composed only of glucose units, and exhibits approximately 17% α-1,1-glucosidic linkages (non-reducing end), 3%

α-1,3-glucosidic linkages, 19% α-1,4-glucosidic linkages, 49% α-1,6-glucosidic linkages, 7% α-1,3,6-glucosidic linkages, and 5% α-1,4,6-glucosidic linkages. IMD has a weight-average molecular weight of approximately 5,000 (**Figure 1**). IMD is highly soluble in water and hardly affects the taste or flavor of the food to which it is added. The dietary fiber content of IMD determined using an enzyme-HPLC method (AOAC 2001.03) was ≥80% on the solid basis[4]. Indigestible dextrin and polydextrose are also soluble dietary fibers comprised of glucose. Compared with these substances, IMD exhibits a unique structure, consisting of only α-glucosidic linkages and exhibiting more α-1,6-glucosidic linkages. Therefore, IMD is expected to have physiological effects distinct from those of indigestible dextrin and polydextrose.

It has been reported that IMD attenuates elevated blood glucose levels after carbohydrate loading[5][6]. However, the effects of IMD on elevated postprandial glucose levels have not yet been reported. Thus, we examined whether IMD contained in bread attenuates elevated blood glucose levels.

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(a) Nonreducing end α-Glcp
(b) 1,3-linked α-Glcp
(c) 1,4-linked α-Glcp
(d) 1,6-linked α-Glcp
(e) 1,3,6-linked α-Glcp
(f) 1,4,6-linked α-Glcp
(g) reducing-end Glcp
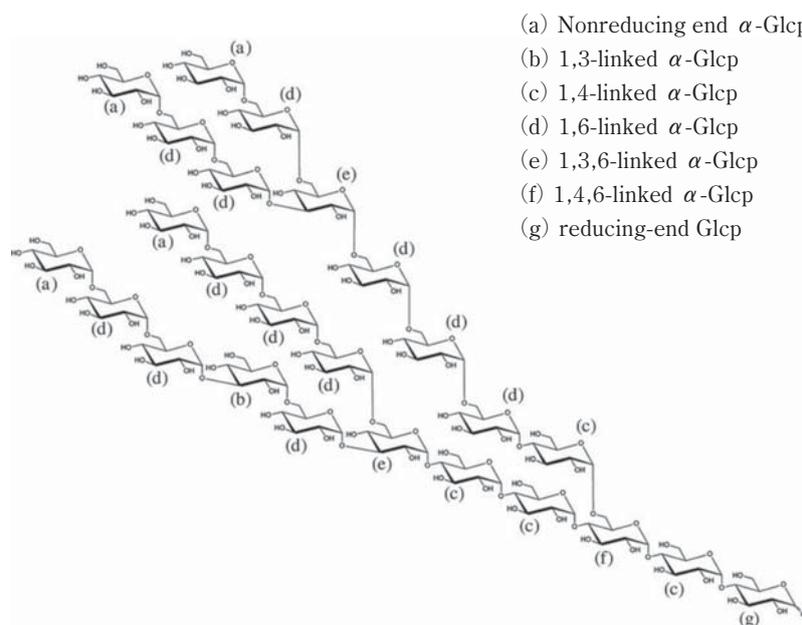
Figure 1.　The putative structure of IMD.

2.　MATERIALS AND METHODS

2.1. Subjects

Subjects were healthy adult (19 male, 11 female) employees of Hayashibara Co., Ltd., who gave consent to participate in the study and met the inclusion criteria. The major inclusion criteria were: no medical history or medication that may have effects on the study. Subjects who met the above requirements and were considered healthy and eligible by the investigator were registered to participate in the study.

Exclusion criteria were in place to enable the selection of healthy subjects likely to show a blood glucose increase within a certain range, while also considering their safety. The following subjects who were suspected to have hypoglycemia (at fasting), postprandial hyperglycemia (120 minutes after intake) or hyperglycemia (at fasting or at random) at each measurement time point were excluded from the analysis: (a) fasting blood glucose levels <60 mg/dL or ≥126 mg/dL[7)8)], (b) blood glucose levels ≥189 mg/dL at 120 minutes after meal[9)], or (c) random blood glucose levels ≥270 mg/dL[8)]. The guidelines used for the above criteria were based on glucose levels in the venous blood. Fasting blood glucose levels were nearly the same between the finger-stick blood collection (capillary blood) performed for this study and routine blood collection (venous blood collected from the elbow); however, a blood glucose level after carbohydrate loading was reported to be up to 1.35-fold higher in the capillary blood than in the venous blood[10)]. Therefore, each criterion after carbohydrate loading was multiplied by 1.35 and

used as a conversion value.

2.2. Test substance

IMD (Hayashibara Co., Ltd., Okayama, Japan) was used as the test substance. The dietary fiber content of IMD determined using the enzyme-HPLC method (AOAC 2001.03) was 86.1% on the dry solid basis (**Table 1a**). Two types of koppepan (similar to a hot dog bun; Bread A not-containing IMD and Bread B containing IMD) were prepared according to a general recipe. Bread B containing IMD contained 2.93 g of IMD on a solid basis. Both Bread A and B weighed about 70 g after baking. The amount of added dietary fiber was not decreased after baking, as confirmed by enzyme-HPLC. The subjects did not seem to be able to distinguish between the test and control meals because IMD is mostly tasteless, colorless, and odorless.

Overnight-fasted subjects consumed breakfast including Bread A or B with jam (AOHATA 55 Portion Jam Strawberry [13 g per cup], AOHATA Corporation, Hiroshima, Japan) and tea beverage (Afternoon Delicious Tea without sugar, Kirin Beverage Company, Limited, Tokyo, Japan) (**Tables 1a** and **1b**). The breakfast contained 2 pieces of Bread A, 2 cups of jam, and 200 mL of tea beverage for a meal without IMD; and 1 piece of Bread A, 1 piece of Bread B, 2 cups of jam, and 200 mL of tea beverage for a meal with IMD (the meal without IMD contained 80.2 g of carbohydrate and 450.4 kcal of total energy)[11)].

2.3. Study design

To unify the study conditions as much as possible across the two intake tests, a pre-specified meal was served for supper on the day before the test and any intake of foods other than the pre-specified meal was prohibited after 6

Table 1a.　Koppepan used for testing

	Content of IMD	Weight before baking
Bread A （not containing IMD）	-	77 g
Bread B （containing IMD）	2.93 g	80 g （including the weight of IMD）

Table 1b.　Test meal

Product name	Koppepan	Strawberry jam	Tea beverage
Ingredients	Flour, baker's yeast, bread quality improving agent, sugar, salt, fat-free milk powder, egg, and margarine（random order） （when preparing bread containing IMD, IMD was added to the above ingredients）	Strawberry, sugars (sucrose, glucose ［liquid］, fructose)/gelling agent (pectin), and acidifier	Black tea（Darjeeling Tea 73%）/flavor, and vitamin C
Nutrition facts Calories Total Carbohydrate Protein Total Fat Sodium	（2 pieces ［bread not-containing IMD］） 408.4 kcal 69.8 g 10.4 g 8.2 g 1.4 g	（2 cups ［13 g per cup］） 42 kcal 10.4 g 0 g 0 g 4 mg	［200 mL］ 0 kcal 0 g 0 g 0 g 12 mg

p.m. on the day before the test in this study. Drinks were also limited to water or barley tea after 6 p.m. in a similar manner. The subjects consumed the pre-specified meal for supper between 6 p.m. and 9 p.m. on the day before the test, and they were not allowed to eat or drink from after supper until the end of the test on the following day. To prevent dehydration, however, subjects were allowed to drink an appropriate amount of water or barley tea prior to the start of the test.

On the day of the test, subjects who were confirmed to be in good health based on the results of both a questionnaire on health eligibility and fasting blood glucose measurements, consumed breakfast (with or without IMD) over the course of 15 minutes. Thereafter, the subjects were kept at rest in a sitting position to the extent possible for about 2 hours until the end of the test. To minimize variability in blood glucose levels, subjects were not allowed to eat or drink anything other than the pre-specified meal during the test. Blood glucose levels were determined by the subjects immediately before (at fasting) and 30, 45, 60, 90, and 120 minutes after meal intake (6 times in total). Test strips (Accu-Chek Aviva Test Strip F, Roche Diagnostics, Basel, Switzerland) of the same lot were used for determination of blood glucose levels. The series of tests were performed for the 2 types of breakfast separately. A washout period of at least one week was allowed between tests.

A total of 30 subjects were divided into two groups by block randomization, and were assigned to one of two intake order groups (without IMD → with IMD, or with IMD → without IMD) in a double-blind crossover fashion.

The assignment list was sealed and strictly kept until the end of the study. Test meals were prepared and labeled by the same person that assigned the subjects to the study groups.

2.4. Evaluation items

Evaluation items included the time course of blood glucose levels from 0 to 120 minutes, change in blood glucose levels from baseline (Δ blood glucose level), area under the blood glucose level-time curve (AUC), and area under the Δ blood glucose level-time curve (Δ AUC). Comparisons were made for maximum blood glucose levels (C_{max}) and maximum levels of Δ blood glucose (Δ C_{max}) between meals with and without IMD.

In addition to an analysis of all subjects, a stratified analysis was also performed for subjects with a tendency for increased postprandial blood glucose levels. A subject with a tendency for increased postprandial blood glucose levels was defined as a subject whose Δ C_{max} was ≧70 mg/dL after intake of a meal without IMD, based on a previous report[5].

2.5. Measurement of the density of aqueous solutions of IMD

The densities of aqueous solutions of IMD and maltodextrin (Pinedex #1, Matsutani Chemical Industry Co., Ltd., Hyogo, Japan), with nearly the same dextrose equivalent (DE) as IMD, were measured. Six different IMD aqueous solutions (10% to 60% ［w/w］) and 4 different maltodextrin aqueous solutions (10% to 40% ［w/w］) were prepared, and their concentrations were precisely determined using a heat drying under reduced pressure method (siliceous earth method). The specific

gravity of each sample solution was measured at 20℃ and 40℃ using a pycnometer. The density of each sample was calculated by multiplying the specific gravity with the density of water (0.9982 g/cm³ at 20℃ and 0.99222 g/cm³ at 40℃). The density of each concentration was calculated by linear regression.

2.6. Ethics

This study was approved by the institutional review board for volunteer studies at Hayashibara Co., Ltd. (approved on December 4, 2017 [Registration No. 210]), and thereafter conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Medical and Health Research Involving Human Subjects under supervision of physicians with an adequate support system. All subjects received complete information on the importance, purpose, and protocol of the study, and signed a consent form regarding participation in the study and publication of the study results.

2.7. Statistical analysis

All values are expressed as mean ± standard deviation (SD). AUC was calculated using the trapezoid formula.

Statistical analysis of data was performed using the Wilcoxon signed-rank test with a p value ≤0.05 (two-sided) being considered statistically significant. Statcel2, an add-in for Microsoft Excel, was used for statistical analyses.

3. RESULTS

3.1. Subjects

Before the study was completed, 2 subjects dropped out of the study due to poor health conditions, resulting in a

**Table 2.** Characteristics of all subjects（n＝28）

Age	41.1 ± 8.6	years
Body height	167.9 ± 6.5	cm
Body weight	64.3 ± 11.1	kg
BMI	22.8 ± 3.3	kg/m²
Body fat percentage	24.4 ± 5.9	%

（mean ± standard deviation）
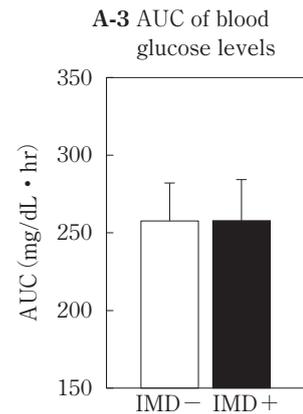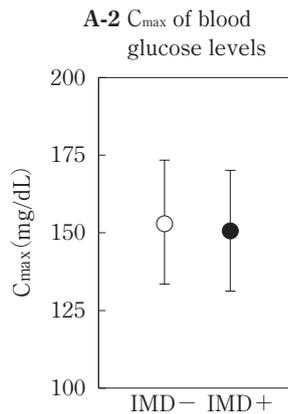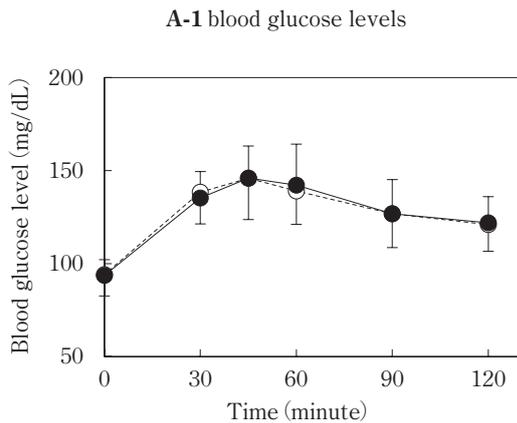
A. Blood glucose levels

A-1 blood glucose levels

A-2 C_{max} of blood glucose levels

A-3 AUC of blood glucose levels

B. Δ Blood glucose levels

B-1 Δ blood glucose levels

B-2 C_{max} of Δ blood glucose levels

B-3 AUC of Δ blood glucose levels
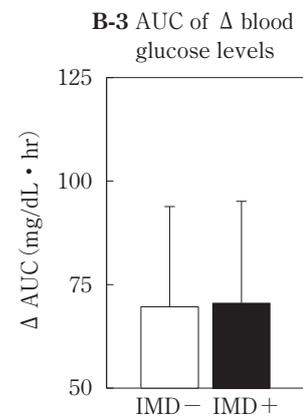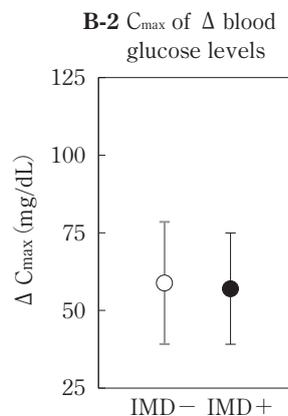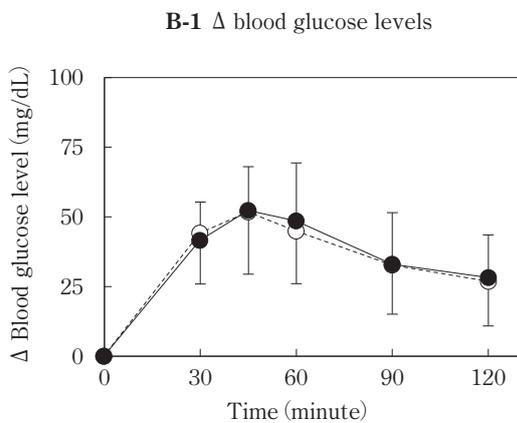
○ or white bar ＝ intake without IMD, ● or black bar ＝ intake with IMD
Mean ± standard deviation（n ＝ 28）

Figure 2. Changes in blood glucose levels over time after breakfast intake（all subjects）

total of 28 subjects (18 male and 10 female) included in the final analysis. The characteristics of all subjects are shown in **Table 2**.

3.2. Blood glucose levels

Blood glucose results for all subjects are shown in **Figure 2**. Postprandial blood glucose levels and Δ blood glucose levels reached a maximum at 45 minutes after intake and gradually declined through 120 minutes after intake, regardless of the addition of IMD. There were no differences in blood glucose levels over time between IMD intake and non-IMD intake.

A stratified analysis was performed to examine the effect of IMD on subjects with a tendency for increased postprandial blood glucose levels. Per the stratification criteria, 7 subjects (4 male and 3 female) whose Δ C_{max} was ≥70 mg/dL after intake without IMD were considered as having a tendency for increased postprandial blood glucose levels. The characteristics of subjects with a tendency for increased postprandial blood glucose levels are shown in **Table 3**.

Results of the stratified analyses are shown in **Figure 3**. Postprandial blood glucose levels and Δ blood glucose levels reached a maximum at 45 minutes after intake without IMD, whereas the time to reach the maximum was delayed to 60 minutes following intake with IMD. Furthermore, the maximum level with IMD at 60 minutes was lower than that without IMD at 45 minutes. Both AUC and Δ AUC were significantly lower following intake with IMD than without IMD ($p = 0.02$ for AUC

Table 3.　Characteristics of subjects with a tendency for increased postprandial blood glucose levels（n ＝ 7）

Age	41.0 ± 10.6	years
Body height	168.8 ± 6.2	cm
Body weight	65.8 ± 12.4	kg
BMI	23.0 ± 3.5	kg/m²
Body fat percentage	25.6 ± 5.6	%

（mean ± standard deviation）
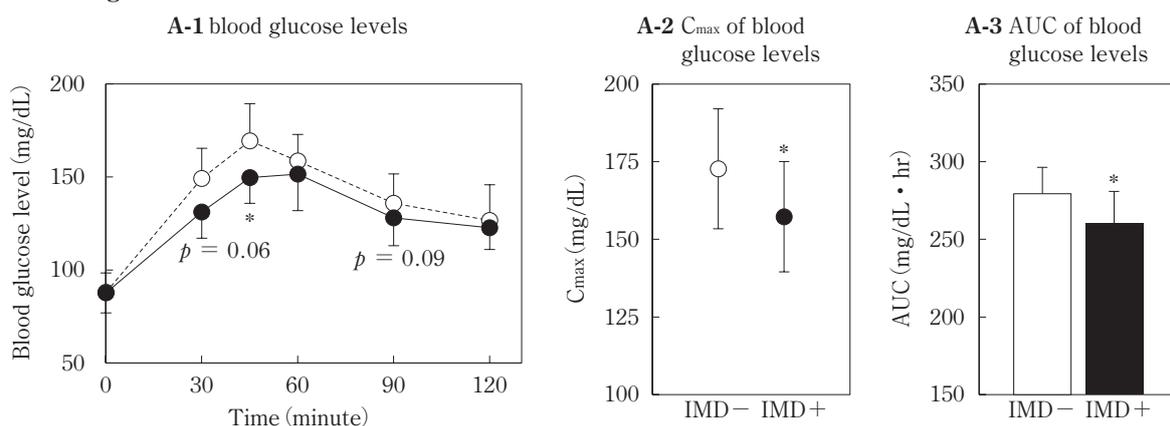
A. Blood glucose levels

A-1 blood glucose levels

A-2 C_{max} of blood glucose levels

A-3 AUC of blood glucose levels

B. Δ Blood glucose levels

B-1 Δ blood glucose levels

B-2 C_{max} of Δ blood glucose levels

B-3 AUC of Δ blood glucose levels
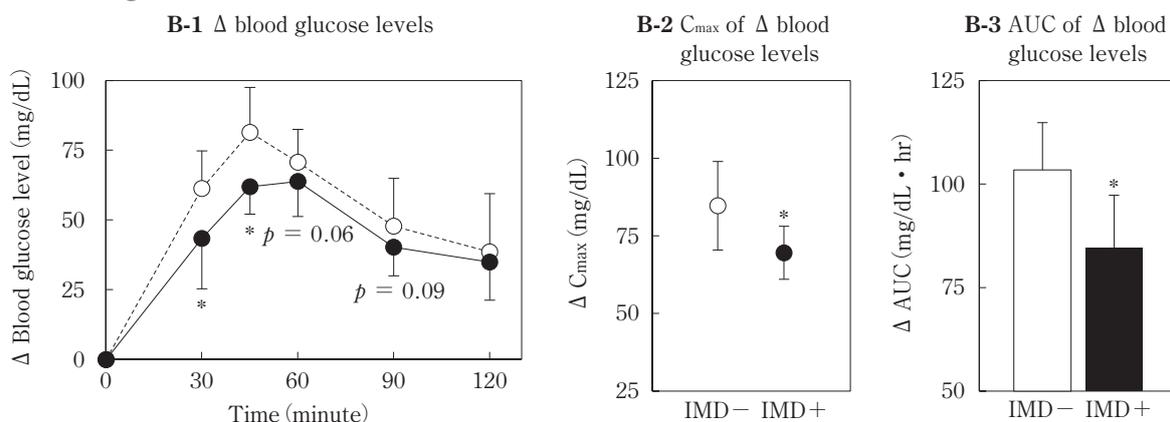
○ or white bar ＝ intake without IMD, ● or black bar ＝ intake with IMD
Mean ± standard deviation（n ＝ 7）　*: Significant difference compared with intake without IMD（p＜0.05）

Figure 3.　Changes in blood glucose levels over time after breakfast intake（subjects with a tendency for increased postprandial blood glucose levels）

Table 4. Density of aqueous solution

Concentration 〔% (w/w)〕	Density ρ_4^t (g/cm³)			
	IMD		Maltodextrin	
	20℃	40℃	20℃	40℃
10	1.0398	1.0332	1.0395	1.0325
20	1.0844	1.0770	1.0837	1.0761
30	1.1323	1.1239	1.1313	1.1230
40	1.1837	1.1744	1.1830	1.1735
50	1.2390	1.2289	-	-
60	1.2985	1.2879	-	-

and $p = 0.02$ for Δ AUC). For the secondary analysis, statistical analyses were carried out at each time point. Results showed that blood glucose levels were significantly lower at 45 minutes ($p = 0.02$) and trended lower at 30 and 90 minutes ($p = 0.06$ and $p = 0.09$, respectively) after intake with IMD compared to intake without IMD. Δ blood glucose levels were significantly lower at 30 and 45 minutes ($p = 0.04$ and $p = 0.02$, respectively), and trended lower at 60 and 90 minutes ($p = 0.06$ and $p = 0.09$, respectively). Furthermore, C_{max} and Δ C_{max} of individual subjects were also significantly lower after intake with IMD compared to intake without IMD ($p = 0.03$ for C_{max} and $p = 0.03$ for Δ C_{max}).

3.3 Density of aqueous solutions of IMD

The densities of aqueous solutions of IMD were measured to determine the presence or absence of water absorbability or swellability, which is the known mechanism of action of common dietary fibers. An aqueous solution of 10% (w/w) IMD was found to have a density of <1.04 g/cm³ at 40℃, similar to that of maltodextrin (**Table 4**).

4. DISCUSSION

The purpose of this study was to examine whether IMD attenuates elevated blood glucose levels following meal intake. In this study, 1 koppepan (Bread B) contained 2.93 g of IMD. Analysis of all 28 subjects found that IMD contained in bread did not show an attenuating effect on elevated blood glucose levels. However, a stratified analysis of 7 subjects with a tendency for increased postprandial blood glucose levels did show an attenuating effect of IMD on blood glucose elevation, consistent with previous studies[6]. Specifically, a stratified analysis of 7 subjects whose Δ C_{max} was ≥ 70 mg/dL without IMD showed significantly lower AUC and Δ AUC (0 to 120 minutes) after breakfast intake containing IMD compared to breakfast intake without IMD. Both blood glucose and Δ blood glucose levels were significantly lower or trended lower from 30 to 90 minutes after breakfast intake with IMD compared to breakfast intake without IMD. Furthermore, C_{max} and Δ C_{max} of individual subjects

were also significantly lower after intake with IMD compared to intake without IMD. Thus, the results suggest that IMD attenuates elevated blood glucose levels following meal intake in subjects with a tendency for increased postprandial blood glucose levels.

Rapid elevation in blood glucose levels is normally attenuated by insulin, which is secreted in response to increases in blood glucose. The 7 subjects that were included in the stratified analysis seem to have had weak functioning in blood glucose regulation. A rapid increase in blood glucose levels is known to increase the risk of cardiovascular events[12]. The attenuating effect of IMD on blood glucose elevation in subjects with a tendency for elevated postprandial blood glucose levels suggests that introduction of IMD into daily life may help to reduce the risk of cardiovascular events.

It is interesting to note that the attenuating effect of IMD on elevated blood glucose levels in the stratified analysis was more remarkable than the effect observed following glucose solution intake (with 5 g of IMD). Results of previous studies demonstrated that the attenuating effect of IMD on elevated blood glucose levels was weaker at 2.5 g of IMD[6] compared with 10 g or 5 g[5] in a dose-dependent fashion in subjects with a tendency for increased postprandial blood glucose levels. In addition to the inhibitory effect of IMD on glucose absorption from the intestine, IMD was also shown to inhibit the activity of maltase and isomaltase, which are small intestinal mucosal enzymes[5]; however, the inhibition rate was only ~10%[5]. Therefore, the attenuating effect of IMD on elevated blood glucose levels seems to be largely attributable to inhibition of glucose absorption. The dose-dependent attenuating effect of IMD on elevated blood glucose levels may be due to the fact that the inhibitory effect on glucose absorption cannot catch up with the amount of supplied glucose that surpasses the effect of IMD. Accordingly, IMD administered with a meal, in which glucose is slowly supplied to the intestine via the digestive process, may efficiently inhibit glucose absorption compared with a glucose solution, in which glucose reaches the intestine at once, and could explain the effects noted above.

Some dietary fibers are known to attenuate elevated postprandial blood glucose levels, and are believed to slow glucose absorption by delaying the transit of ingested food into the intestine by either increasing the viscosity of the ingested food or as a result of their inherent water-absorption/swelling actions, resulting in attenuation of elevated blood glucose levels[13]. As IMD exhibits a low viscosity[5], the effect of IMD viscosity on slowing of glucose absorption is likely to be small. The density of an aqueous solution of IMD was not remarkably high at 40℃ (which is close to the temperature of the human body), and even at a concentration of 10% (w/w) there is a high concentration of IMD in feces[14], suggesting that swelling or related water-absorption of IMD is minimal. Therefore, it is likely that IMD inhibits glucose absorption by a different mechanism from that of other dietary fibers. It is known that glucose is absorbed from the intestine via a glucose transporter[15][16]. Future studies are necessary to examine the effect of IMD on the glucose transporter.

5. CONCLUSIONS

In conclusion, IMD attenuates elevated blood glucose levels following meal intake in subjects with a tendency for increased postprandial blood glucose levels. Introduction of IMD into daily life may offer health benefits. The attenuating effect of IMD on elevated blood glucose levels is considered to be the result of inhibition of glucose absorption via a mechanism of action distinct from that of dietary fibers, i.e., increasing viscosity or water-absorption/swelling.

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