Original Article 診療と新薬 2018; 55: 217–224

診療と新薬 Web

Efficacy of Jerusalem Artichoke in Healthy Japanese with Postprandial Plasma Glucose Level:

A Randomized, Double-blind, Placebo-controlled Study

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● **Abstract**

Objective: The objective of this study is to examine how the ingestion of Jerusalem artichoke containing inulin contributes to inhibiting the increase of postprandial plasma glucose level.
Methods: A randomized, placebo-controlled, double-blind study was conducted to elucidate how the ingestion of a supplement made from the Jerusalem artichoke containing inulin lowers blood glucose level. In this study we measured the postprandial plasma glucose level after OGTT as the primary outcome. Furthermore, adverse events were collected by means of a written questionnaire during the study.
Results: From all of 61 applicants, 13 were eliminated due to not-meeting inclusion criteria. The 48 subjects were randomly assigned to an intervention group and made a start with ingestion. 21 were withdrawn due to fever or business, and the remaining 27 subjects completed the study. Thus, data obtained with 27 subjects (KK: 14〈M; 5, F; 9〉, Placebo: 13〈M; 3, F; 10〉) was used for the analysis of efficacy. At Visit 1 (0-week) and Visit 3 (12-week), a significant difference was observed between two groups; the changes from FPG to 0.5 h-OGTT. At 0-week, KK did not present a significant difference in 2 h-OGTT, meanwhile Placebo yielded a significant increase. Also, at 12-week, KK decreased compared to FPG in 2 h-OGTT, while no decrease was observed in Placebo. No adverse effects were observed after the ingestion of the test product.
Conclusion: We found out that the ingestion of the supplement made from Jerusalem artichoke containing inulin contributed to inhibiting the increase of postprandial plasma glucose level. In addition, no safety-related matter occurred during the test period.

Key Words : Jerusalem artichoke, inulin, plasma glucose level

1. INTRODUCTION

According to "National Health and Nutrition Survey" conducted by the Ministry of Health, Labor and Welfare ("MHLW") in 2016[1)], the estimated numbers of both the prevalence of diabetes and the risk of developing diabetes are about 10 million people in Japan. Diabetes, along with hypertension or dyslipidemia, are often called "Lifestyle-related diseases", and it is said that one of the major causes for these diseases is obesity triggered by dietary habits and/or the lifestyle habits of modern people[2)]. As the basic direction for comprehensive implementation of national health promotion, the MHLW implemented the movement called "Health Japan 21"[3)]. Since the control of blood glucose level is important to prevent the diabetes, Glycemic index (GI)[4)], the index determining the effect of different foods on blood glucose, came to public attention. The active consumption of foods with low GI can contribute to preventing a rapid increase in blood glucose level.

Potatoes are regarded as a popular source of dietary carbohydrate worldwide, and are generally considered to be a high glycemic index (GI) food[5)]. Jerusalem artichoke, on the other hand, contain little starch, and are delicious tubers that act quite similarly to potatoes when cooked. The main ingredient of Jerusalem artichoke is the soluble fiber called Inulin[6)], and therefore they are considered as a low GI food[7)]. The consumption of Jerusalem artichoke can contribute to inhibiting the elevation of the postprandial glucose levels and is also expected to fend of diabetes.

However, in Japan the cultivation area of Jerusalem artichoke is limited, and this fact hinders easy ingestion in our daily life. If there is a supplement-type of Jerusalem artichoke which is dried and powdered, it will promote distribution and enable us to intake them more easily in our daily life.

In this study, we conducted a randomized, placebo-controlled, double-blind study to verify the efficacy of the supplement containing Jerusalem artichoke for postprandial plasma glucose level, by using healthy Japanese adults as test subject. At the same time, we also

1) JACTA (Japan Clinical Trial Association)
2) AKASAKA FREUDE CLINIC
3) GRANDE CO., LTD.

examined the safeness of ingesting the supplement.

2. METHODS

2.1. Trial design

A randomized, placebo-controlled, double-blind study was conducted with the aid of a fund GRANDE CO., LTD. (Fukuoka) at Japan Clinical Trial Association (JACTA, Tokyo). The baseline examination was performed for the applicants between May and June, 2017. Based upon this examination, the screening and the assignment was carried out. Then, the intervention started on June 24th until September 16th, 2017 (12 weeks). This study was conducted in accordance with the ethical principles of the declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Pharmaceutical Law Wisdoms (Tokyo). Written informed consent was obtained from all Subjects. This trial was registered at UMIN Clinical Trial Registry (Trial ID: UMIN000027027).

The allocation of the test product to the subjects was carried out by the person in charge of allocation. The allocation list was sealed and strictly controlled in a safe deposit box of JACTA until the end of the study.

2.2. Subject

Healthy subjects participated in the present study. All of the subjects in this study were public volunteers who had enrolled in the monitor bank of TRIBELATE CORPORATION (Tokyo), recruited from April through June, 2017.

2.2.1. Inclusion criteria

(1) Healthy Japanese males and females aged between 20 and 59 years;
(2) Individuals fasting plasma glucose (FPG) level less than 126 mg/dL;
(3) Individuals postprandial plasma glucose (PPG) level 2 hours after oral glucose tolerance test, 2 h-OGTT less than 200 mg/dL.

2.2.2. Exclusion criteria

(1) Subjects with food allergies;
(2) Subjects who are pregnant or lactating;
(3) Subjects who consume medicinal product which may influence the outcome of the study;
(4) Subjects who consume food which may influence the outcome of the study;
(5) Subjects who are judged as unsuitable for the study by the principle investigator.

2.3. Randomization

From all 61 applicants, 13 were eliminated according to the exclusion criteria. The inclusion /exclusion criteria was judged by the principle investigator. All subjects were sequentially allocated to Group A (n = 23, M; 9, F; 14) and Group B (n = 25, M; 11, F; 14) using a random number table. In the process of subject assignment, background factors such as gender, age, and FPG were taken into consideration to avoid biased distribution. Subjects in Group A ingested placebo and subjects in Group B ingested the test sample for 12 weeks.

Table 1 Ingredient (ratio)

Item	KK	Placebo
Jerusalem artichoke roasted powder	59.4%	−
Jerusalem artichoke powder	39.6%	−
Calcium stearate	1%	−
Lactose	−	84%
Indigestible dextrin	−	10%
Crystalline cellulose	−	5%
Magnesium stearate	−	1%
Total	100%	100%

2.4. Description of test foods and blinding

The test product was “Kin-no-KIKUIMO” (“KK”) containing inulin prepared by GRANDE CO., LTD. The amount of daily intake was 7 tablets (1 tablet weighs 250 mg, therefore 7 tablets weigh 1,750 mg), which include inulin 750 mg per day. The Placebo does not include Jerusalem artichoke or inulin. Both tablets were indistinguishable in shape, color, or taste, and were managed by an identification symbol. All involved were blinded. **Table 1** shows ingredient of the samples.

2.5. Experimental procedures

2.5.1. Experimental protocol

Subjects consumed 7 tablets of the supplement with hot or cold water per day before dinner for 12 weeks. Clinical visits were scheduled every 6 weeks at Higashikoganei Sakura Clinic, Tokyo. They consumed the tablets just before consuming loading food on the visit of 6w and 12 w. Subjects were instructed as follows: to take the assigned supplement as indicated; to maintain their usual lifestyles and habits; to avoid excessive amounts of food, drink, and alcohol; to maintain a daily record of every meal eaten and to use a pedometer during the test period; and to send the diary to the study coordinator.

2.5.2. Outcome

The objective of this study is to elucidate the effect on lowering blood glucose level by consuming the Jerusalem artichoke containing inulin. To evaluate this objective, the postprandial plasma glucose level after OGTT (Oral glucose tolerance test) was measured as the primary outcome. Furthermore, other blood biochemical parameters were recorded to evaluate the safety of KK, and adverse events were collected by means of a written questionnaire during the study. According to the schedule shown in **Table 2**, we measured parameters on efficacy and safety.

During every clinical visit, the subjects would have their blood taken four times to check plasma glucose levels. 12 hours prior to the visit, the subjects were not allowed to eat or drink (except water). The subjects took a 10 minute rest before proceeding with the first blood extraction to check blood biochemical parameters and glucose levels. Then, the subjects would eat 2 rice balls

Table 2　Schedule for the study

Item \ Term	Pretrial test	Screening	Test period	
			6 w	12 w
Informed consent	●	●		
Selection and/or allocation	●	●		
Blood extraction (4 times)	●	●	●	●
OGTT	●	●	●	●
Biochemical parameters	●	●	●	●
Ingestion of test foods			↔	↔
Log			↔	↔

● :Implementation
↔ :Daily practice during the test period

(equal to 75 g dextrose grape sugar) and the second blood test was taken 30 minutes after eating. Two more tests followed an hour and 2 hours after eating to check glucose levels. The trial procedure of the test day is shown in **Figure 1**.

2.6. Data analysis

A full analysis set (FAS) was adopted in the study and no sample size design was used. All statistics were expressed as mean ± standard deviation (SD). For the blood plasma level and blood biochemical parameters, Student's t-test was used for intergroup comparisons of changes from the baseline. Changes from the baseline in the same group were assessed using paired t-test. A chi-square test and Student's t-test were used to compare subject backgrounds between groups.

Multiplicity according to the occasions was not adjusted. Any subjects with missing values were eliminated from the analysis. Statistical analyses were performed using Statcel 4 (Yanai, 2015) and Excel Tokei 2015 (SSRI). The results were considered significant at a $< 5\%$ level in the two-sided test.

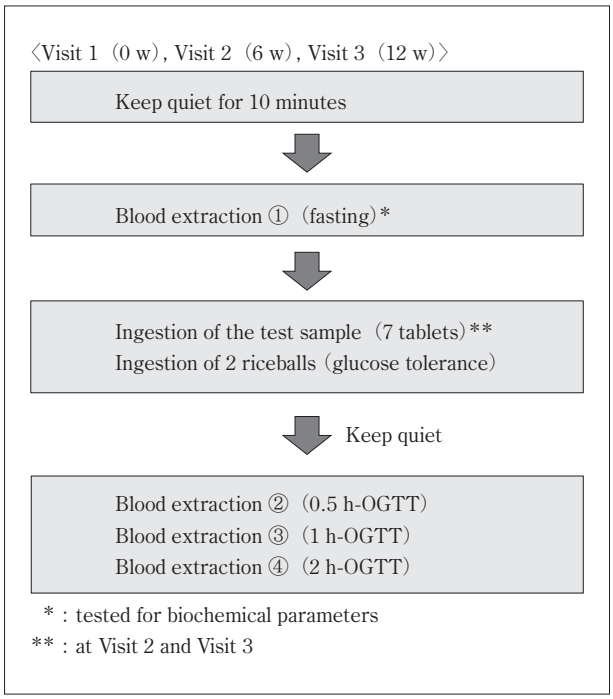

Figure 1　Trial procedure of the test day

3. RESULTS

3.1. Participant demographics

The 48 subjects were randomly assigned to an intervention group and made a start with ingestion. 21 subjects were withdrawn due to business or fever, and the remaining 27 subjects completed the study. Thus, data obtained with 27 subjects (KK: 14 〈M; 5, F; 9〉, Placebo: 13 〈M; 3, F; 10〉) was used for the analysis of efficacy (**Figure 2**). There was no significant difference in gender, age, or FPG (0 w) between groups (**Table 3**).

3.2. Postprandial plasma glucose

Table 4 shows the results of OGTT. At Visit 1 (0-week) and Visit 3 (12-week), a significant difference was observed between two groups from FPG to 0.5 h-OGTT. As for Visit 2 (6-week) of intergroup analysis, KK suppressed OGTT more than Placebo, but a significant difference was not found. At 0-week, KK did not represent a significant difference in 2 h-OGTT, meanwhile Placebo yielded a significant increase. Also, at week 12, KK decreased compared to FPG in 2 h-OGTT. On the other hand, there was no decrease in Placebo.

3.3. Biochemical blood test

Table 5 shows the blood biochemical parameters (⊿ 0-12 w). In the blood biochemical parameters data, one subject's level of CK (CPK) was recorded too high as a data collection mistake. Therefore this data was not used in the results of this study, so therefore 26 subject's (KK: 14 〈M; 5, F; 9〉, Placebo: 12 〈M; 2, F; 10〉) data was evaluated. With respect to the blood biochemical test, no significant difference was observed in KK after 12 weeks of ingestion. In Placebo, Total bilirubin, AST (GOT), ALT (GPT), and Calcium showed a significant difference. γ-GT (γ GTP) (males and females), Total cholesterol, and Neutral fat (TG) of placebo at week-0 as well as ALT

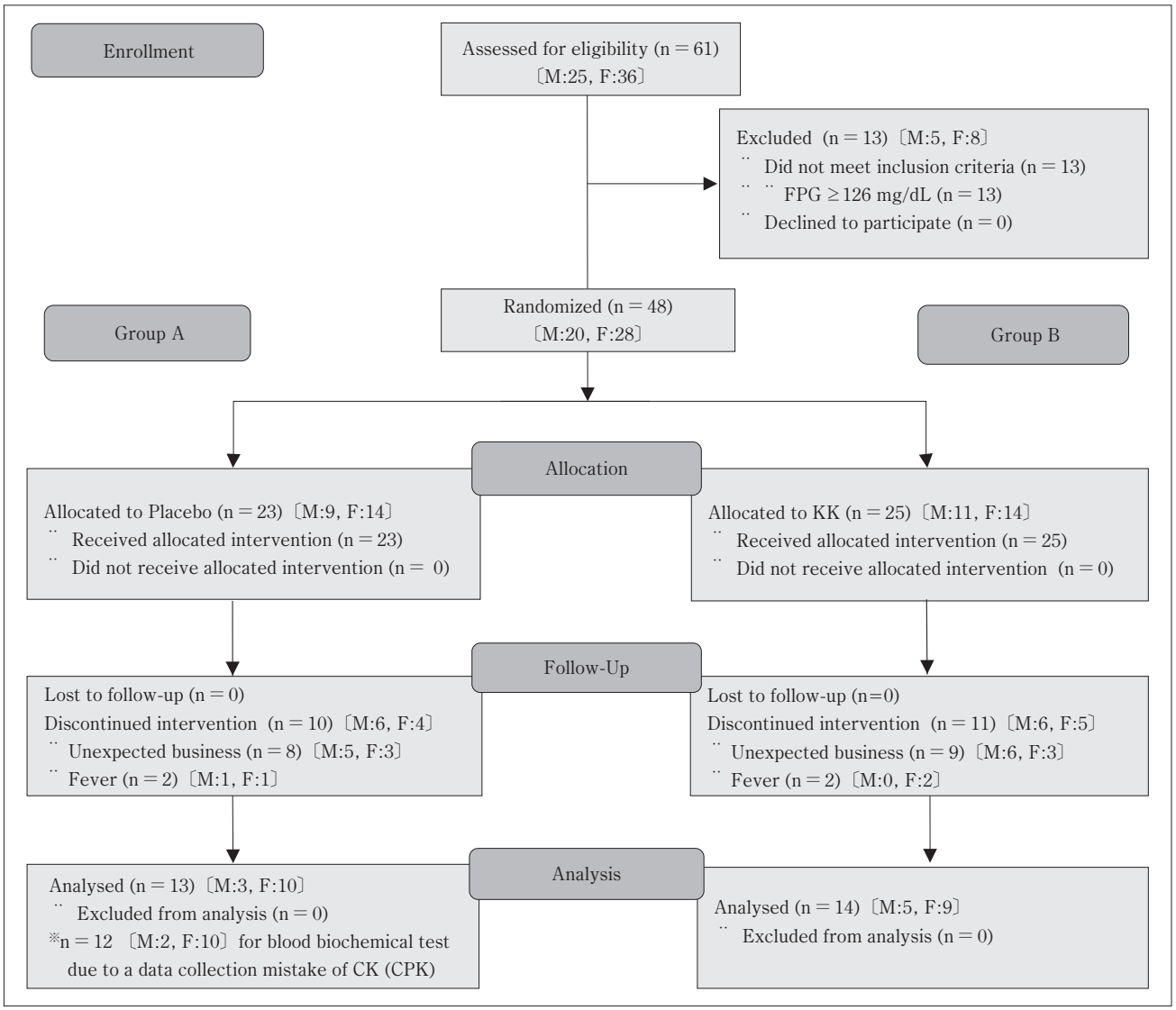

Figure 2 Flow diagram of subject disposition

Table 3 Subject demographics

Item	Unit	KK	Placebo
Subjects	numbers	14	13
Male: Female*	numbers	5:9	3:10
Age*	years	40.3 ± 11.3	47.1 ± 8.3
FPG (0 w)*	mg/dL	94.0 ± 13.8	93.7 ± 11.0

mean ± SD

*No significant difference

(GPT) of placebo at week-12 were not found to remain within the normal range (data not shown). However, the principle investigator judged it as the range of physiological variation (or clinically safe).

3.4. Safety

No adverse effects associated with the test product were observed in the course of the reporting.

4. DISCUSSION

We conducted a randomized, placebo-controlled, double-blind study for examining the efficacy of the supplement of Jerusalem artichoke containing inulin, for the lowering of postprandial plasma glucose level.

As the primary outcome, after 12-weeks of ingestion of the test product, while the postprandial plasma glucose

Table 4　Postprandial blood glucose

Item (Time points)		Values[1]		P-value[2]
		KK (n = 14)	Placebo (n = 13)	
0-week	FPG	94.0 ± 13.8	93.7 ± 11.0	0.038#
	0.5 h-OGTT	129.9 ± 28.0**	148.8 ± 28.3**	
	⊿ FPG-0.5 h	35.9 ± 23.3	55.2 ± 22.4	
	1 h-OGTT	121.9 ± 27.9**	136.3 ± 35.9**	0.176
	⊿ FPG-1 h	27.9 ± 22.8	42.6 ± 31.6	
	2 h-OGTT	98.5 ± 20.6	105.8 ± 19.8**	0.190
	⊿ FPG-2 h	4.5 ± 15.2	12.1 ± 13.9	
6-week	FPG	92.9 ± 16.2	90.8 ± 11.4	0.177
	0.5 h-OGTT	132.9 ± 37.0**	145.2 ± 29.2**	
	⊿ FPG-0.5 h	40.1 ± 26.9	54.4 ± 26.5	
	1 h-OGTT	120.1 ± 35.6**	130.2 ± 29.7**	0.214
	⊿ FPG-1 h	27.3 ± 24.4	39.3 ± 24.6	
	2 h-OGTT	95.4 ± 23.0	97.5 ± 21.7	0.466
	⊿ FPG-2 h	2.5 ± 14.4	6.6 ± 14.5	
12-week	FPG	94.1 ± 29.6	92.9 ± 12.1	0.024#
	0.5 h-OGTT	121.2 ± 35.5*	147.5 ± 30.4**	
	⊿ FPG-0.5 h	27.1 ± 35.4	54.6 ± 22.1	
	1 h-OGTT	112.6 ± 30.3*	129.2 ± 36.9**	0.142
	⊿ FPG-1 h	18.5 ± 30.8	36.3 ± 30.2	
	2 h-OGTT	92.1 ± 15.4	95.0 ± 24.0	0.603
	⊿ FPG-2 h	− 2.0 ± 24.5	2.1 ± 13.9	

Values are expressed as the mean ± SD.

1) *$p < 0.05$, **$p < 0.01$ against FPG

2) #$p < 0.05$ between-group difference in change from FPG

level after OGTT among Placebo showed an abrupt increase in blood glucose level, the increasing level of KK was significantly inhibited.

In addition, as the secondary outcome, no adverse effects associated with the test product were observed in the course of the reporting, and the safety of ingesting the test product was suggested by the results of blood biochemical analysis and inquiries.

Main Findings

This study examined the effectiveness of ingesting the supplement made from Jerusalem artichoke which contains inulin as its main ingredient, for the lowering of postprandial plasma glucose level. At Visit 1 (0-week) and Visit 3 (12-week), significant difference was observed between two groups of the changes from FPG to 0.5 h-OGTT. At 0-week, KK did not represent a significant difference in 2 h-OGTT, meanwhile Placebo yielded a significant increase. Also, at week 12, KK decreased compared to FPG in 2 h-OGTT, while no decrease was observed in Placebo.

The increase in postprandial plasma glucose level is caused when the digested starch changes into glucose, then it is absorbed from the small intestine and is mixed into the blood circulation. For healthy people, insulin is secreted immediately after the mixture, and it turns the glucose in the blood into the glycogen. Then the glycogen is stored in various organs. Therefore, the glucose level in the blood returns to a normal level two hours after the meal. On the other hand, if the secretion of insulin is insufficient, the performance of insulin is not appropriate, or the excessive amount of glucose is ingested after the meal, it becomes hard for the blood glucose level to decrease[8)9)]. The long-term continuance of the status of high blood glucose level can cause diseases such as diabetes.

In this study the result among Placebo showed that from week 0 through week 12, just 0.5 h after glucose tolerance the blood glucose level suddenly increases, and returns to the normal level after 2 h. Although KK showed a similar tendency, the increasing rates of blood glucose level 0.5 h after the glucose tolerance are significantly lower than those of Placebo. In addition, as for the blood glucose level after 2 h, while the level of Placebo increased compared to the level before the

Table 5 Changes in biochemical blood test

Item	Unit	Gender	Time points	KK (n = 14) 〔M:5, F:9〕	Placebo (n = 12) 〔M:2, F:10〕
Total bilirubin	mg/dL	M/F	⊿ 0-12 w	− 0.07 ± 0.15	0.13 ± 0.17 [a,c]
Total protein	g/dL	M/F	⊿ 0-12 w	− 0.1 ± 0.3	0.1 ± 0.3
Albumen	g/dL	M/F	⊿ 0-12 w	− 0.1 ± 0.2	0.0 ± 0.2
AST (GOT)	U/L	M/F	⊿ 0-12 w	− 0.1 ± 1.7	5.2 ± 7.4 [a,b]
ALT (GPT)	U/L	M/F	⊿ 0-12 w	− 0.8 ± 4.8	7.2 ± 8.6 [a,c]
ALP	U/L	M/F	⊿ 0-12 w	0.8 ± 16.5	2.8 ± 26.5
LD (LDH)	U/L	M/F	⊿ 0-12 w	4.4 ± 18.3	5.8 ± 17.6
γ-GT (γ GTP)	U/L	M	⊿ 0-12 w	− 1.0 ± 6.2	19.5 ± 9.2 [b]
		F	⊿ 0-12 w	0.8 ± 6.6	− 11.2 ± 46.8
CK (CPK)	mg/dL	M	⊿ 0-12 w	16.8 ± 18.8	− 1.0 ± 9.9
		F	⊿ 0-12 w	4.6 ± 27.7	− 5.6 ± 9.4
Total cholesterol	mg/dL	M/F	⊿ 0-12 w	− 1.5 ± 18.4	4.1 ± 16.9
Neutral fat (TG)	mg/dL	M/F	⊿ 0-12 w	4.6 ± 25.8	− 41.4 ± 185.1
Sodium	mEq/L	M/F	⊿ 0-12 w	− 0.1 ± 1.1	0.3 ± 2.3
Chloride	mEq/L	M/F	⊿ 0-12 w	0.0 ± 1.8	0.4 ± 1.8
Potassium	mEq/L	M/F	⊿ 0-12 w	− 0.1 ± 0.3	− 0.1 ± 0.3
Calcium	mg/dL	M/F	⊿ 0-12 w	0.0 ± 0.3	0.2 ± 0.2 [a]
Inorganic phosphorus	mg/dL	M/F	⊿ 0-12 w	0.1 ± 0.5	0.1 ± 0.4
Urea nitrogen	mg/dL	M/F	⊿ 0-12 w	− 0.5 ± 3.9	0.5 ± 1.8
Creatinine	mg/dL	M	⊿ 0-12 w	− 0.02 ± 0.07	0.03 ± 0.01
		F	⊿ 0-12 w	0.02 ± 0.03	0.02 ± 0.06

Values are expressed as the mean ± SD.

[a] $p < 0.05$ against 0-week.

[b] $p < 0.05$, [c] $p < 0.01$ between-group differences in change from 0-week.

glucose tolerance, the data of KK showed the decreased level compared to before the glucose tolerance after 12 weeks of ingestion. Therefore, it is speculated that the ingestion of KK contributed to the inhibition of the increase rate of the blood glucose level after 0.5 h, and the continuous ingestion of KK enhances the decreasing rate of the blood glucose level after 2 hours.

This test product is the supplement consisting of the dried powder of Jerusalem artichoke. The tubers of Jerusalem artichoke are rich in inulin, which makes the plant one of the primary inulin resources[10) 11)]. It is well-known that inulin can impart certain nutritional and therapeutic benefits which can improve our health conditions and reduce the risk of many lifestyle related diseases, and there are many study reports that supports these functionalities[12)].

Inulin is categorized as a water soluble dietary fiber in nutriology. Inulin is a batch of fructan of polysaccharide, and this polysaccharide is a polymer of fructose[13)]. It cannot be decomposed in human digestive organs, however it is metabolized in the microflora of a human's large bowel. Since it is equipped with the high water-retention capacity, swelling capacity and oil-holding capacity[14)], it turns into a gel once dissolved in water and eases the movements of foods from the stomach to the small intestines. At that time, it wraps around the carbohydrates or fats which are ingested at the same time and moves them to the small intestines while avoiding digestion. Eventually, this function slows down the speed of absorbing carbohydrates and inhibits the sudden increase of postprandial plasma glucose level[15)].

Based upon the discussion above, we can speculate that the function of inulin contained in the test product contributed to the inhibition of the increase level of postprandial plasma glucose level.

Secondary Findings

In this study, we conducted the blood biochemical analysis and inquiries as a secondary endpoint, and the results revealed that no abnormal change caused by the test product was observed during the ingestion period. As for the blood test, Total bilirubin, AST (GOT), ALT (GPT), and Calcium showed significant difference between two groups, and ALT (GPT), γ-GT (γ GTP), Total cholesterol and Neutral fat (TG) of Placebo exceeded the normal range. On the other hand, no significant difference was observed in KK after 12 weeks of ingestion. The investigator judged it as the range of physiological variation (or clinically safe).

During the test period 21 subjects discontinued the test. 17 of them discontinued the test due to an unexpected business matter, whereas the other 4 stopped the test because of illness (cold). However, both have nothing to do with the ingestion of the test product. In addition, the diary of the subject did not show any adverse events.

Therefore, the results of the medical interview, blood test, and determination of adverse events all suggested there was no adverse influence associated with the test product. These results indicated the safety of the ingestion of the test product for the 12-week test period.

General Information

Normally, the blood glucose level increases when we ingest foods. On the other hand, however, the abnormally-high level of postprandial plasma glucose level can not only increase the risk of developing diabetes, but also expose the blood vessel to oxidant stress as a result of the production of active oxygen and eventually cause the risk of arteriosclerosis. Arteriosclerosis often causes high blood pressure, which can eventually trigger Myocardial infarction and/or stroke[16)17)]. In addition, the residual glucose in the blood which is not consumed as an energy is transported to the fat tissues and stored as fat; this can be one of the major causes of obesity[18)]. Furthermore, the condition of postprandial hyperglycemia is reported to increase the risk of dementia[19)]. Therefore, the increase in the postprandial plasma glucose level can trigger the risks of various diseases even among healthy people.

To combat the above problems, previous studies reported a wide variety of possible preventative measures in our daily life, such as ingesting foods with low GI, applying the "second-meal[20)]", and/or changing of the pattern of ingestion (such as "Vege-first"). If healthy people, along with the above-explained measures, use the easily-prepared supplement in daily life and inhibit the increase rate of postprandial plasma glucose level, they can reduce the risk of diseases and extend healthy life expectancy.

In addition, inulin contained in the test product has functions of normalizing the condition of the microflora and maintaining the intestinal environment[21)]. In addition, it is also reported that the ingestion of inulin can decrease the amount of serum cholesterol and neutral lipid, and this supports that inulin can control the lipid metabolism[22)23)]. Therefore, the ingestion of the test product can contribute to the prevention of obesity thanks to not only the effect of inhibiting the increase of postprandial plasma glucose level but also improving the intestinal environment or the lipid metabolism. In sum, it is highly speculated that the above-discussed functions eventually lower the risk of previous mentioned diseases.

Limitations

In this study we examined the effect of inhibiting the increase of postprandial plasma glucose level by OGTT testing. The increase rate of postprandial plasma glucose level differs substantially between individuals. Since this study focused on the inhibiting effect against the increase of the blood glucose level, it only discussed the differences between prior-glucose tolerance and post-glucose tolerance in OGTT. However, in order to discuss the individual differences between testing subjects, the difference of fasting blood glucose level should be also considered. Therefore, it is necessary for the further study to increase the number of subjects and conduct the test study that includes the comparison of the glucose tolerance level performed by the tests such as stratified analysis of fasting blood glucose level. In addition, the functional mechanism of the ingredients other than inulin in Jerusalem artichoke is unknown, and this point is desirably considered for further scrutiny.

5. CONCLUSION

In conclusion, we found out that the ingestion of the supplement made from Jerusalem artichoke which contains inulin as its main ingredient for 12 weeks contributed to inhibiting the increase of postprandial plasma glucose level. In addition, no safety-related matter occurred during the test period.

CONFLICT OF INTEREST

All parts of this study were funded by GRANDE CO.,LTD. Otoha Ueki is an employee. All authors state that the study was conducted in the absence of any other relationships that could be interpreted as a conflict of interest.

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（Table 1 was corrected in July 2018.）