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Sea Tangle Supplementation Alters Intestinal Morphology in Streptozotocin-induced Diabetic Rats and Lowers Glucose Absorption

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Abstract This study examined whether dietary supplementation with sea tangle alters the intestinal morphology of streptozotocin-induced diabetic rats and affects the glucose absorption rate. Forty male Sprague-Dawley rats were divided into 2 groups and fed either a control (AIN76-based) diet or a sea tangle-supplemented diet. After 3 weeks, 10 rats in each group received an intramuscular injection of streptozotocin (45 mg/kg BW), and feeding was continued for 3 additional weeks. Dietary supplementation with sea tangle resulted in a lower fasting plasma glucose level compared with the control diet in diabetic rats. Scanning electron micrographs revealed serious damage to the jejunal villi of diabetic rats fed the control diet, whereas supplementation with sea tangle alleviated the damage. In a separate experiment, 20 male Sprague-Dawley rats were divided into 2 groups and fed either a control diet or a sea tangle-supplemented diet for 5 weeks, and fasted rats were subjected to *in situ* single-pass perfusion. The glucose absorption rate determined in the absence of digesta was decreased by 34% in the jejunum of rats fed a sea tangle diet compared with those fed a control diet. In conclusion, sea tangle supplementation lowered glucose absorption rate, altered intestinal morphology, and appeared to protect villi from damage caused by diabetes mellitus.

Keywords: sea tangle, intestinal morphology, glucose absorption, diabetes

Introduction

Diabetes mellitus is a chronic disease associated with serious complications, and its incidence is increasing worldwide. Control of blood glucose level is the primary concern for diabetic patients. Intensive glycemic control is essential for risk reduction of diabetes-related complications, which are the major causes of premature death among those with diabetes (1). Natural products such as mushrooms have long been used as traditional medicine for diabetes (2), and studies have revealed single or multiple mechanisms of action for some natural products. Although their popularity varies among people of different ethnicities, products with high soluble fiber content are known to protect against diabetes (3).

Sea tangle (*Laminaria japonica*) is widely used as food and as a seasoning in Korea and Japan. Dry sea tangle is composed of 12.3% moisture, 7.4% protein, 41.1% carbohydrate, 34% ash, and 29.3% dietary fiber (4); it possesses large quantities of alginic acid, which is classified as a soluble non-starch polysaccharide. Supplementation with sea tangle powder or extracts produced hypoglycemic and hypolipidemic effects in streptozotocin-induced diabetic rats (5-7). As shown by Kimura *et al.* (8), low-molecular-weight sodium alginate (50 and 100 kDa) as well as natural sodium alginate (2,700 kDa) isolated from a *Laminaria* species enhanced glucose tolerance and fecal excretion of cholesterol. Lee and Lee (9) found that, among various dietary fibers, alginic acid was the most effective at slowing glucose movement across a dialysis membrane.

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Carbohydrate digestion directly increases the postprandial blood glucose level, and the degree of carbohydrate digestion depends on the intestinal morphology, enzymes, and types of carbohydrates involved (10). Intestinal epithelium is a very dynamic tissue that adjusts its rate of cellular proliferation to meet changing digestive demands. Dietary fiber has an overall trophic effect on intestinal muscle. It has been reported that diabetes itself induces hyperplasia and hypertrophy of the small intestine (10, 11). Some investigators have speculated that alterations in the morphology of the small intestine produce enzymatic effects that may contribute to postprandial hyperglycemia in diabetes (10, 12).

We hypothesized that sea tangle powder supplementation in the diet may affect the morphology of intestinal villi, which may in turn decrease the glucose absorption rate. Scanning electron microscopy (SEM) has been used clinically to investigate bowel function (13). In addition, modifications in the structure of the gastrointestinal mucosa are often used to evaluate gut function in response to particular food components (14). Of the various perfusion techniques developed to assess uptake across the intestinal mucosa in eutherian laboratory animals, the 'single-pass' method is the most widely used and has the lowest variability (15). Therefore, we examined the morphology of jejunal villi in streptozotocin-induced diabetic rats and normal rats, which were fed either a sea tangle-enriched diet or a control diet, using SEM. We also tested whether sea tangle supplementation in the diet affects the glucose absorption rate in the jejunum, using *in situ* single-pass perfusion.

Materials and Methods

Animals and diets Forty male Sprague-Dawley rats

(Daehan Biolink Co., Eumseong, Chungbuk, Korea), weighing 200-220 g each, were housed individually in stainless steel mesh cages in a room maintained at 22±2°C and 60-65% relative humidity, with a normal 12-hr light/dark cycle. The rats were fed a commercial diet (Jinyang Co., Gyeongsan, Gyeongbuk, Korea) and tap water *ad libitum* for 1 week prior to the experiment. After 1 week of acclimation, the rats were randomly divided into 2 groups (n=20 each). The experimental group received a sea tangle-supplemented diet, which was based on an AIN76 diet (16) supplemented with 15% sea tangle powder (Table 1). This level of sea tangle supplementation provides approximately 5% dietary fiber. The control group received the control diet (AIN76), which contained 5% cellulose. At 21 days after beginning the diets, the rats from each group received an intramuscular injection of either streptozotocin (STZ; 45 mg/kg BW in 0.1 M citrate buffer, pH 4.5) or citrate buffer (n=10 each). The rats were maintained on the respective diets for 3 additional weeks, for a total feeding period of 6 weeks. The diet ingredients were purchased from Harlan Terklad Co. (Madison, WI, USA). Dry sea tangle was washed with water to remove salt and contaminants, dried under hot air, ground into a fine powder, and passed through a 50-mesh filter.

SEM sample preparation The rats were anesthetized by diethyl ether inhalation. The abdomen was opened, and the small bowel was excised and stripped away from the stomach to the ileocecal valve. At one-third of the total bowel length, a proximal 2 cm segment was resected for SEM.

Observation of jejunal morphology by SEM The jejunum specimens were split longitudinally and pinned flat, mucosal side up, in phosphate-buffered saline (PBS). The tissue was prefixed in a fixation solution (2.6% glutaldehyde, 0.8% paraformaldehyde, 0.1 M PBS, pH 7.4) at 4°C for 24 hr and then washed with 0.1 M PBS. Post fixation was carried out in 1% osmium tetroxide for 2 hr. The samples were dehydrated in ethanol and isoamylacetate, then critical-point dried, and coated with 300 gold in an ion coatee (IB5; Eiko Engineering Co., Ibaraki, Japan). Observations were made by SEM (S-4100; Hitachi, Tokyo, Japan) at 15 kV accelerating voltage (17).

Table 1. Composition of experimental diets (g/kg diet)

Ingredient	Control diet	Sea tangle diet
Casein	200	200
DL-Methionine	3.5	3.5
Corn starch	150	50
Sucrose	400	400
Corn oil	50	50
Lard	100	100
Alpha-cellulose	50	0
Mineral mix.[1)]	35	35
Vitamin mix.[2)]	10	10
Choline bitartrate	1.5	1.5
Sea tangle powder[3)]	0	150

[1)]AIN-76 mineral mixture (Harlan Teklad).
[2)]AIN-76 vitamin mixture (Harlan Teklad).
[3)]15% sea tangle powder contains approximately 5% dietary fiber.

***In situ* single-pass perfusion** After 1 week of adaptation, 20 male Sprague-Dawley rats (Daehan Biolink Co., Korea), weighing 40-50 g each, were divided into a sea tangle group and a control group (10 rats each) and fed the corresponding diets (Table 1) for 5 weeks. The rats were fasted for 15-16 hr prior to each experiment and anesthetized by intraperitoneal injection of 50%(w/v) urethane solution. *In situ* single-pass perfusion was carried out according to the method of Oh *et al.* (18). Body temperature was maintained by laying the rats on a slide warmer. The abdomen was opened, an inlet cannula was inserted into the jejunum at 3-4 cm below the Treitz ligament, and an outlet cannula was inserted into the lower part of the jejunum, 10 cm from the upper part. The jejunal lumen was then washed with 0.9% NaCl to remove the contents, and silicon tubing (Cole-Parmer Instrument Co., Vernon Hills, IL, USA) was connected into the upper and lower cannulae. The jejunal lumen was then perfused with phosphate buffer (pH 6.5) containing 0.5 mM glucose and 0.03 mM phenol red as a nonabsorbable marker, at a flow rate of 0.2 mL/min at 37°C. Steady state was achieved in approximately 30 min. After 30 min of perfusion, single-pass perfusion was repeated 4 times at 15-min intervals, and each perfusate was analyzed for glucose. The average was determined in order to calculate each animal's glucose absorption rate.

Glucose analysis The concentration of glucose was measured as absorbance at 505 nm using the glucose oxidase method and a commercially available enzymatic kit (Embiel Co., Gunpo, Gyeonggi, Korea).

Statistical analysis The results are presented as means ± standard deviations. Group means were compared by Duncan's multiple range test after preliminary analysis of variance (ANOVA). Differences were considered statistically significant at $p<0.05$. Differences between the 2 groups were analyzed by Student's *t*-test. All statistical tests were performed using SPSS for Windows (SPSS, Chicago, IL, USA; version 10.0).

Results and Discussion

Body weight gain and plasma glucose Although there was a significantly decreased weight gain in streptozoticin-induced diabetic rats compared with normal rats, body weight gains were not significantly different between the control and sea tangle groups regardless of whether the group is normal or diabetic. Food efficiency ratio was decreased by streptozotocin treatment, but was not affected by dietary supplementation of sea tangle powder (Table 2). The sea tangle diet, compared with the control diet, resulted in a lower fasting plasma glucose level in the diabetic rats, whereas there was no difference between the two diets in the normal rats (Table 3). The length of the

Table 2. Effect of sea tangle powder supplementation on weight gain, food intake, and FER in normal rats and streptozotocin-induced diabetic rats

Group[1)]	Weight gain (g/week)	Food intake (g/day)	FER[3)]
Normal-control	15.5±9.82[a1)]	14.97±1.69[ab]	0.17±0.08[a]
Normal-sea tangle	16.8±6.93[a]	15.07±1.04[ab]	0.17±0.05[a]
Diabetic-control	24.8±6.65[b]	14.65±1.11[ab]	-0.22±0.08[b]
Diabetic-sea tangle	23.5±4.36[b]	15.77±1.44[a]	-0.22±0.13[b]

[1)]Values shown are mean±SD (n=10).
[2)]Values in the same column not sharing a common superscript are significantly different between the groups ($p<0.05$).
[3)]Food efficiency ratio.

Table 3. Effect of sea tangle powder supplementation on length of small bowel and fasting plasma glucose in normal rats and streptozotocin-induced diabetic rats[1)]

Group[1)]	Length of small bowel (cm)	Fasting plasma glucose (mg/100 mL)
Normal-control	84.5±6.05[c]	150.9±32.4
Normal-sea tangle	91.5±5.81[b]	164.2±21.9
Diabetic-control	92.3±6.90[b]	446.9±37.8
Diabetic-sea tangle	94.1±8.70[a]	375.5±29.3*

[1)]Values shown are mean±SD (n=10); Values in the same column not sharing a common superscript are significantly different between the groups ($p<0.05$); *Significantly different from the diabetic-control group by *t*-test ($p<0.05$).

small intestine was significantly increased in the diabetic rats compared with the normal rats, and sea tangle supplementation increased the length of the small intestine in not only the diabetic rats but also in the normal rats (Table 3).

It has been reported that the weight of the small intestine increases in spite of a reduction in body weight in untreated diabetic rodents, and this increase in weight has been attributed primarily to elongation of the bowel and greater mucosal and muscle mass (19).

The growth of the small intestine in diabetic rats was found to be most pronounced in the proximal portion, primarily as a result of increased mucosal area (20). There was an increase in the height of the villi in the jejunum of diabetic rats compared with control rats (10, 21). Diabetic rats fed a fiber-rich diet were shown to exhibit pronounced growth of the small intestine, whereas intestinal growth was considerably reduced in diabetic rats fed a fiber-free diet, and diabetic intestinal growth was paralleled by the plasma glucagons-like peptide 2 (GLP-2) level (22). Adachi *et al.* (10) reported intestinal hyperplasia in not only a type 1 diabetic rat model (i.e., STZ-administered rats) but also a type 2 diabetic rat model (OLETF and GK), and transcription factors related to intestinal proliferation (Cdx1) and differentiation (Cdx2) were found to be highly expressed in diabetic rats. In that study, increases in total sucrase and isomaltase activities in diabetes mellitus were said to result from intestinal hyperplasia.

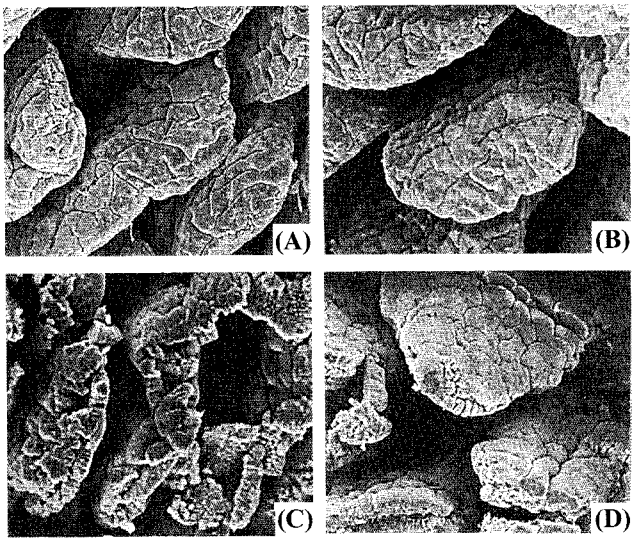

Fig. 1. Scanning electron micrographs of the jejunal mucosal surface (100×). Normal-control (A), normal-sea tangle (B), diabetic-control (C), and diabetic-sea tangle (D).

Jejunal morphology Scanning electron micrographs of the jejunum of the normal and diabetic rats fed either the control or sea tangle diet for 6 weeks are shown in Fig. 1. Normal rats fed the control diet (Fig. 1A) showed regularly arranged, long villi, and normal rats fed the sea tangle diet (Fig. 1B) showed typical leaf-shaped villi with comparatively more surface wrinkles; neither group showed signs of damage. In contrast, the villi of diabetic rats fed the control diet (Fig. 1C) were twisted and varied in shape, and some were collapsed as well as damaged. The diabetic rats that received sea tangle supplementation (Fig. 1D) showed less damage.

Significant surface damage to the villi of the small intestine following lignin supplementation has been shown by SEM (23); however, in the present study, sea tangle supplementation did not result in surface damage of the jejunal villi compared with the control diet, which contained cellulose, in normal rats. Rather, sea tangle supplementation appeared to protect the jejunal villi of diabetic rats from damage.

Glucose absorption rate As shown in Fig. 2, the glucose absorption rates in 10 cm jejunal segments from rats fed the control or sea tangle diet were 37.8 and 24.9%, respectively, reflecting a decrease of 34% in rats fed sea tangle compared with the control rats. The *in situ* single-pass perfusion experiment was carried out in normal rats instead of diabetic rats, because diabetic rats were tried but not able to tolerate the stress caused by the surgery and *in situ* perfusion.

Brown algae contain large quantities of alginic acid. When natural sodium alginate is orally administered, it is converted to free alginic acid in the stomach; however, free alginic acid is not absorbed from the small intestine. Torsdottir *et al.* (24) reported that daily dietary supplementation with 5.0 g of sodium alginate in noninsulin-dependent diabetic patients resulted in significantly lower postprandial increases in blood glucose, serum insulin, and plasma C-

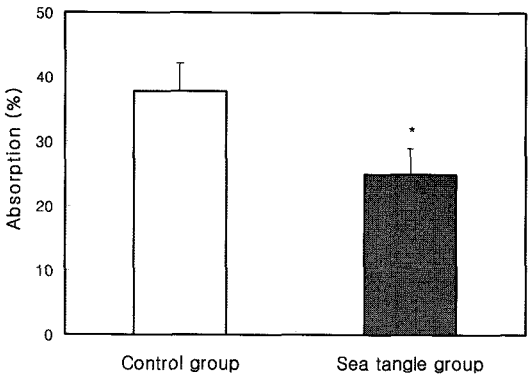

Fig. 2. Glucose absorption rate during perfusion of a glucose solution through the jejunum in normal rats fed the control or sea tangle diet. Glucose absorption rates were measured by *in situ* perfusion of 10 cm jejunal segments and are expressed as the percentage of glucose lost from the perfusate after 15 min. Values shown are mean±SD (n=10); Significant at $p<0.05$.

peptide. They suggested that the effects of sodium alginate on cholesterol excretion and glucose tolerance may be attributable to the inhibition of cholesterol and glucose absorption from the small intestine by gelling of the free alginic acid converted in the stomach. Highly viscous alginate from *Laminaria digitata* dramatically reduced the glucose absorption rate in pigs, whereas non-starch polysaccharides extracted from the red algae *Palmaria palmata* (dulse) and *Eucheuma cottonii* did not affect intestinal glucose absorption (25).

In the presence of soluble dietary fiber, which increases the viscosity of the intestinal contents, physical mixing is replaced by simple diffusion (26). This reduces the rate at which the nutrients appear in the circulation, and exposure of the gut surface to the nutrients is increased, triggering the release of such regulatory hormones as GLP-2, which stimulates mucosal cell growth (22). GLP-2 is a proglucagon-derived peptide secreted from enteroendocrine L-cells, which are predominantly located in the ileum and the proximal part of the colon (22). Plasma levels of the potent insulin secretagogue GLP-1, insulin, and C-peptide were increased after oral glucose with ingestion of a high-fiber diet compared with a fiber-free diet (20).

Flourie *et al.* (27) showed that, in healthy humans, pectin impairs intestinal absorption by means of increased unstirred layer resistance. They explained that diminished glucose absorption would be less likely due to a modification of the absorbing cell membrane itself than to a decrease in the intraluminal diffusion of glucose.

Soluble dietary fiber such as alginic acid may stimulate the growth of goblet cells or increase secretory activity so that mucin protects the epithelium from damage caused by diabetes. Intestinal mucins are high molecular mass glycoproteins which form a highly hydrated mucus coat along the epithelial surface of the intestinal tract. It has been speculated that oat bran, rye bran, and soybean hull supplementation result in higher goblet cell secretory activity in both the proximal and distal small intestine of hamsters (28). Alginate induces mucin secretion in isolated vascularly perfused rat colon (29).

Lee and Lee (9) compared the retarding effects of various dietary fibers on glucose movement across a dialysis membrane and found that it increased as follows: alginic acid, guar gum, carboxymethylcellulose, citrus pectin > apple pectin > α-cellulose. The greater the inhibition of glucose movement through the dialysis membrane, the more effectively the human blood glucose level was controlled. Soluble dietary fiber acts like a sponge, binding water, nutrients, bile acids, and carcinogens as they pass along the gastrointestinal tract. However, in the present study, glucose absorption rates were determined when fiber was not physically present. In our *in situ* single-pass perfusion experiment, the jejunal lumen was washed with 0.9% NaCl to remove the contents and perfused with a phosphate buffer containing glucose. Given that there was no direct physical contact between the dietary components and glucose during perfusion, the lowered absorption rate may have resulted from an altered morphology and/or an altered physical environment, such as a thickened unstirred water layer around the intestinal epithelium in the rats fed a sea tangle-supplemented diet. Then, it is also possible that absorption rate of other water-soluble nutrients decreases with sea tangle supplementation.

Sharp *et al.* (30) stated that in early diabetes, before the onset of hyperplasia, there is a greater driving force for sodium-dependent brush border membrane sugar transport together with increased sodium-independent glucose cotransporter (GLUT2) activity at the basolateral membrane, promoting sugar movement across enterocytes. Reimer *et al.* (20) compared the effect of cellulose and a highly fermentable rhubarb fiber with cellulose fiber on the level of proglucagon mRNA and *in vitro* small intestinal glucose transport in normal rats. They found that, although the ileal proglucagon mRNA levels were significantly higher and passive permeability was significantly lower in rats fed rhubarb fiber than in those fed cellulose fiber, the maximum transport rates of glucose and the expression of the sodium-dependent glucose cotransporter (SGLT-1) and GLUT2 were unaffected by diet. Therefore, it is unlikely that the decreased glucose absorption rate observed in this study in the sea tangle-fed group is related to glucose transporters in the epithelium of the small intestine.

It has been reported that small intestinal hyperplasia and the resultant increase in total disaccharidase activity might be one reason for postprandial hyperglycemia in diabetes mellitus (10) and that the activity is suppressed by consuming dietary fiber (31). In our study, the lowered absorption rate does not appear to be related to a change in disaccharidase activity because the perfusate contained only glucose.

In conclusion, sea tangle supplementation decreased blood glucose, owing in part to a lowered glucose absorption rate possibly attributable to an altered physical environment, such as a thickened unstirred water layer and/or an altered intestinal morphology. Moreover, sea tangle, as compared with cellulose, seems to protect intestinal villi from damage caused by diabetes mellitus.

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