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Review article

Fructooligosaccharide: Metabolism through Gut Microbiota and Prebiotic Effect

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Abstract

This review aims to provide the accurate information with useful application of Fructooligosaccharide (FOS) for health care specialists including dietician and physician, food adviser and user. Therefore, we described on metabolism through gut microbiota, physiological functions including prebiotic effect and accelerating defecation, practical application and suggestions on FOS. FOS is a mixture of oligosaccharides what one to three molecules of fructose are bound straightly to the fructose residue of sucrose with β-1,2 linkage. FOS which is produced industrially from sucrose using enzymes from *Aspergillus niger*, is widely used in processed foods with claimed health benefits. But, FOS occurs naturally in foodstuffs including edible burdock, onion and garlic, which have long been part of the human diet. Therefore, eating FOS can be considered a safe food material. FOS ingested by healthy human subjects, does not elevate the blood glucose and insulin levels, because it is not digested by enzymes in the small intestine. However, FOS is metabolized by gut microbiota to short chain fatty acids, which acidify the environment in the gastrointestinal tract, as well as carbon dioxide, hydrogen and methane. The repeated ingestion of FOS leads to good intestinal microflora with a high proportion of *Bifidobacterium* and a low proportion of putrefactive microbiota. This brings about beneficial health effects such as facilitating defecation, repressing pathogenic bacteria, reducing hepatic responsibility from detoxification, decreasing decomposing matter and improving stool condition. FOS should be contributed to suppress cancer and senescence and to improve the immune response through good intestinal microflora. Thus, FOS can promote health by preventing metabolic syndrome and act as prebiotics to help beneficial microbiota proliferate.

Keywords: Fructooligosaccharide; Gut Microbiota; Prebiotic Effect; Health Benefit

Abbreviations

FOS: Fructooligosaccharide

FoSHU: Foods for Specified Health Uses

Introduction

Fructooligosaccharide (FOS) was made from sucrose using a specific enzyme from *Aspergillus niger* in1982 [1,2] and developed as a low energy bulking sweetener with a sweetness of about 30% of sucrose. FOS which is manufactured enzymatically from sucrose is a mixture of 1-kestose (39 %), nystose (53 %) and 1^F-β-fructofuranosyl-nystose (7 %), which is formed respectively from one, two and three molecules of fructose bound linearly to the fructose residue of sucrose with β-1,2 linkage, with the remaining 1% consisting of glucose and sucrose. The structural formulae of the FOS components are shown in Figure 1.

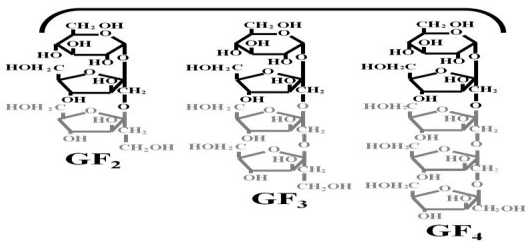

Figure 1: Structure of components of fructooligosaccharide made enzymatically from sucrose.

FOS is classified as a nondigestible oligosaccharide; it is not digested by enzymes in the human small intestine, and issued in many processed foods as a food material with health benefit at the present time. FOS was initially named "Neosugar" by the developer and a Neosugar association was established to promote its application in Japan. The name "Neosugar" was also used in the first academic paper on FOS [3]. However, when an application was made for FOS to be classified under "Foods for Specified Health Uses (FoSHU)" in Japan, the Ministry of Health, Labor and Welfare decided not to use the term "Neosugar", as a proper noun for the product. Therefore, the trade name was changed to "Fructooligosaccharide", which has been used ever since.

A new Japanese classification system for "Foods with Function Claims" was launched in 2015 [4]. This differs from being classified under "FoSHU". "Foods with Function Claims" are foods submitted to the Secretary-General of the Japanese Consumer Affairs Agency as products whose labels bear function claims based on scientific evidence, under the responsibility of the food business operator. Before purchasing and consuming these products, consumers can carefully check the warnings on the product label and the information disclosed on the website of the Consumer Affairs Agency. FOS is often an important ingredient of "Foods with Function Claims".

The nondigestible oligosaccharides forming FOS are widely distributed in nature and are contained in foodstuffs such as edible burdock, onion, garlic and banana [5,6]. Therefore, eating FOS has long been part of human life and can be considered a safe food material. In addition, acute and subacute toxicity tests using animals on FOS manufactured industrially support the use of FOS as a safe food ingredient [7,8]. FOS, a white odorless powder, is a non-reducing saccharide. It is easily dissolved in cold water and is more resistant than glucose and fructose to Maillard reactions [1,9]. The quality of the pleasant sweet taste of FOS is similar to that of sucrose. The use of FOS for cooking and processed foods is similar to that of sucrose, because their physicochemical properties are similar.

This review aims to provide the accurate information of FOS for health care specialists including dietician and physician, food advisers and users to utilize correctly and effectively FOS-containing foods with health benefit. Therefore, we would like to describe on metabolism through gut microbiota, practical application and suggestions on FOS, and then to discuss the specific functions of FOS focusing on prebiotic effect and accelerating defecation.

Metabolism of Fructooligosaccharide Through Gut Microbiota

It has been demonstrated in tracer experiments using [^{14}C]-FOS that about 60% of FOS administered orally to conventional rats is metabolized to CO_2 over 24 h, although FOS is not digested by enzymes in the small intestine. The primary evidence is that gut microbiota performs an important role in the metabolism of FOS [10].

When [^{14}C]-sucrose, which is readily digested by small intestinal sucrase, was administered orally to conventional rats, about 60% of the sucrose was metabolized to [^{14}C]-O_2 in 24 h after administration and excreted from the body. When [^{14}C]-FOS, which is not digested by small intestinal enzymes, was administered orally to conventional rats, like sucrose, about 60% of FOS was metabolized to [^{14}C]-O_2 in 24 h and excreted from the body. However, the [^{14}C]-O_2 excretion lagged 5-6 h after the [^{14}C]-O_2excretion of sucrose (Figure 2). This time lag seems to be the period during which FOS is being transferred to the lower intestine and converted to short chain fatty acids by gut microbiota, which are then further metabolized by the host to produce energy. These results were contrary to expectations, because FOS which is not hydrolyzed by small intestinal enzymes to monosaccharides was metabolized to carbon dioxide as well as sucrose.

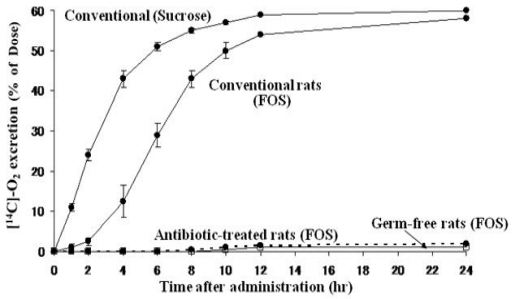

Figure 2: Cumulative expired [^{14}C]-O_2 after oral administration of [^{14}C]-FOS or [^{14}C]-sucrose to conventional, antibiotics-treated and germ-free rats.[^{14}C]-FOS (74 kBq per 4 mg/0.4 mL) dissolved in 0.9% NaCl solution water was administered orally to conventional, antibiotic-treated and germ-free rats (body weight about 230 g). Immediately after administration, rats were transferred to an individual metabolic cage made from glass that had a circulating system. [^{14}C]-sucrose (111 kBq per 4 mg/0.4 mL) was used as the control. Each point represents the mean and SEM for three to four rats. FOS, fructooligosaccharide.

To clarify these unexpected results, [^{14}C]-FOS was administered orally to rats treated with a mixture of 50 units/mL of benzylpenicillin potassium, 2.0 mg/mL of neomycin sulfate and 0.5 mg/mL of cefoperazone sodium salt, which decreased the number of gut microbiota. As shown in Figure 2, although [^{14}C]-O_2 excretion was observed in conventional rats, [^{14}C]-O_2 excretion during 24 h after administration was negligible in rats decreased the number of gut microbiota. This showed that FOS was not metabolized to [^{14}C]-O_2 in rats decreased gut microbiota. Furthermore, [^{14}C]-FOS administered orally to germ-free rats as well as to rats treated with antibiotics was scarcely metabolized to [^{14}C]-O_2 during 24 h [10].

These results demonstrate clearly that FOS administrated orally, is metabolized by gut microbiota and used by the host as an energy source. Therefore, gut microbiota is closely involved

in metabolizing non digestible carbohydrates including FOS. In addition, the fact that [^{14}C]-FOS administered orally to germ-free rats and antibiotics-treated rats was scarcely metabolized to [^{14}C]-O_2 demonstrates that FOS administered orally is not hydrolyzed to monosaccharides even under the acidic conditions in the stomach.

Fermentation and Available Energy of Fructooligosaccharide

Resistant oligosaccharides including FOS are fermented by gut microbiota to produce short chain fatty acids such as acetic, propionic and *n*-butyric acids, carbon dioxide, hydrogen, methane, amino acid and vitamin [11]. The short chain fatty acids produced from resistant oligosaccharides are absorbed immediately in the lower intestine and further metabolized by the host to produce energy. This supposition is supported by studies where [^{14}C]-acetic acid, [^{14}C]-propionic acid and [^{14}C]-^{n}-butyric acid injected directly into the cecum of conventional rats were metabolized spontaneously to [^{14}C]-O_2 [10]. Figure 3 illustrates the metabolic pathway of FOS through the gut microbiota.

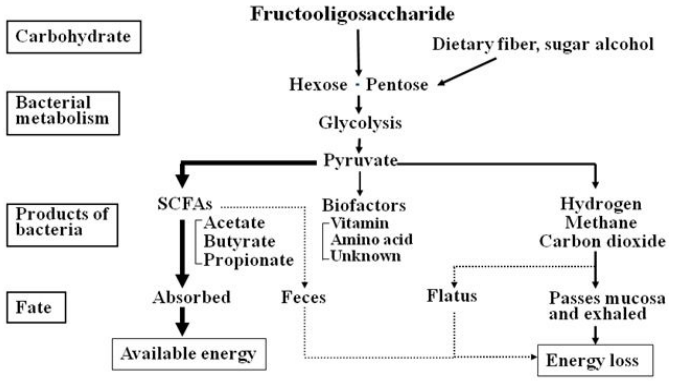

Figure 3: The metabolic pathway of fructooligosaccharide through gut microbiota.

As is the case with rats, FOS ingested by healthy human subjects, does not elevate the blood glucose and insulin levels, because it is not digested by enzymes in the small intestine (Figure 4). However, FOS is completely fermented by gut microbiota, and the short chain fatty acids, used by the host as an energy source, are produced spontaneously. Thus, although FOS is not digested by small intestinal enzymes as well as dietary fiber, it contributes to energy supply through the gut microbiota. The available energy of FOS has been evaluated practically as about 2 kcal/g (8.368 kJ/g) [12-15], a value half that of sucrose. The energy coefficients in Table 1 are practically used for other sugar substitutes in Japan. FOS is a low energy bulking sweetener compared with sucrose. Most resistant oligosaccharide materials already developed are metabolized through gut microbiota and utilized as an energy source as well as FOS. Dietary fiber materials are also partially utilized by gut microbiota and contribute to the host as a source of energy.

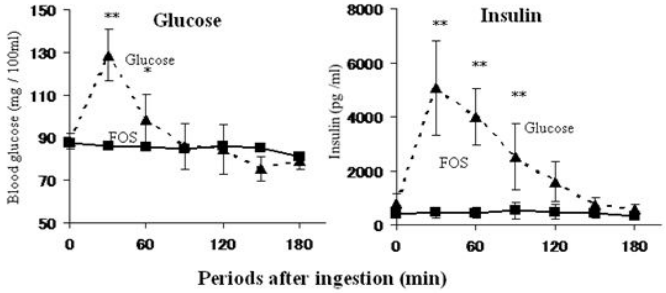

Figure 4: Change of blood glucose and insulin levels after ingestion of fructooligosaccharide in healthy male subjects. There were significant differences between 40 g of glucose and 20 g of FOS in serum glucose and insulin at *: $p<0.05$, and **: $p<0.01$, respectively (n=12). FOS, fructooligosaccharide.

Table 1 Energy coefficients of sugar substitutes in Health Promotion Act in Japan

Energy coefficients (kcal/g)	Sugar substitutes
0 (<0.5)	erythritol
1 (0.5～1.4)	(polydextrose)
2 (1.5～2.4)	sorbose, mannitol, tagatose, maltitol, isomaltitol, palatinit, lactitol, maltotritol, lactulose, galactosyl-sucrose, 4'-galacto-oligosaccharide, 6'-galacto-oligosaccharide, xylo-oligosaccharide, genti-oligosaccharide, fructo-oligosaccharide
3 (2.5～3.4)	sorbitol, xylitol, palatinose-oligosaccharide, soybean-oligosaccharide
4 (> 3.5)	glucose, fructose, galactose, sucrose, maltose, isomaltose, lactose, trehalose, palatinose, trehalulose, coupling-sugar

When FOS is fermented by gut microbiota, hydrogen which is a specific product of fermentation is excreted by expiration (Figure 5) [10-15]. The hydrogen excreted in the breath can be used to evaluate the available energy of resistant carbohydrate as an indicator of fermentation by gut microbiota. In addition, many studies have reported that hydrogen can play important roles on the antioxidant, anti-inflammatory and other protective effects [16-18]. Therefore, hydrogen which is produced from resistant carbohydrates by gut microbiota may electively and directly scavenge hydroxyl radical and prevent a lifestyle-related diseases. The amount of hydrogen excreted depends on how much arrives at the large intestine and the fermentability. Therefore, the amount of hydrogen excreted is greater for FOS, which is scarcely digested by small intestinal enzymes than for is omaltooligosaccharide, which is readily digested [19]. Galactosylsucrose is partially digested by enzymes in the small intestine.

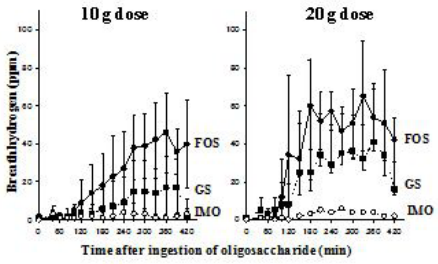

Figure 5: Comparison with breath hydrogen excretion of three oligosaccharides with different digestibility in healthy humans. Data were expressed mean and S.D. of 8-13 subjects. FOS, Fructooligosaccharide; GS, galactosylsucrose; IMO, isomaltooligosaccharide.

Prebiotic Effects of Fructooligosaccharide

Prebiotics are defined as nondigestible carbohydrates (their main component) that have selective effects on gut microbiota [20]. The ingestion of resistant oligosaccharides can confer various health benefits by improving the composition of gut microbiota. Probiotics are defined as live microorganisms that, administered in adequate amounts, can confer health benefits on the host. Strains belonging to *Bifidobacterium* and *Lactobacillus*, the predominant groups of gastrointestinal microbiota, are used most widely as probiotic bacteria and are included in many health promoting foods and supplements. The concept of synbiotics combines both functions of prebiotics and probiotics; an example is a yogurt containing a nondigestible oligosaccharide such as FOS.

Gut microbiota of one thousand types and numbering 100 trillion inhabit the human gastrointestinal tract and make up its intestinal microflora [21]. Intestinal microflora consists of beneficial microbiota such as *Bifidobacterium* and *Lactobacillus*, harmful microbiota such as pathogenic *Escherichia coli* and *Clostridium perfringens* and opportunistic microbiota. The number and proportion of gut microbiota are affected by the human environment, age, stress level, sex and especially intake of meals. The proportion of *Bifidobacterium* is very high in infants, especially that breast feeding, but the proportion of *Bifidobacterium* decreases and *Clostridium perfringens* increases as humans age (Figure 6) [22].

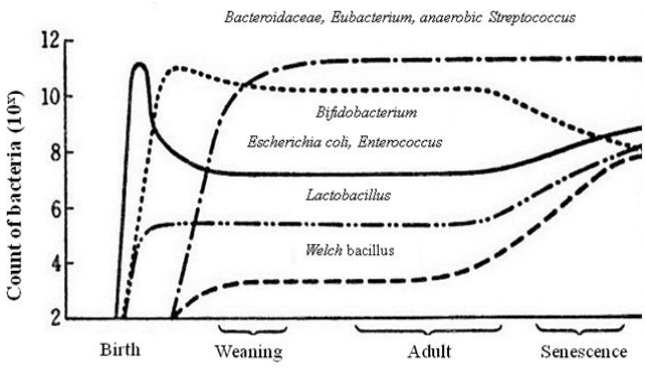

Figure 6: Change of intestinal microflora by aging.

The FOS ingested passes through the small intestine and arrives at the large intestine where it is completely fermented by gut microbiota. The large amount of short chain fatty acids produced by gut microbiota changes the environment in the gastrointestinal tract to acidic conditions (less than pH 7) after repeated ingestion of FOS. The proliferation of pathogenic microbiota is suppressed, because pathogenic microbiota is not resistant for acidic condition. So, the numbers and proportions of pathogenic microbiota decrease gradually and the beneficial microbiota such as *Bifidobacterium* and *Lactobacillus*, which are more resistant to acidic conditions, steadily increase in numbers and proportion [22-25]. A function that improves the composition of intestinal microbiota is the prebiotic effects of FOS.

Figure 7 shows that the repeated ingestion of FOS increases the proportion of *Bifidobacterium* in the elderly and ceasing its ingestion easily returns the intestinal microflora to its former condition [5,26,27]. Much evidence has been reported that the environment in the gastrointestinal tract is improved by the repeated ingestion of 3-10 g of FOS for 1-2 weeks [5,26-38]. Improving the composition of gut microbiota also brings about health benefits such as facilitating defecation, repressing pathogenic bacteria, reducing hepatic responsibility for detoxification, decreasing decomposing matter and improving stool condition. In particular, it has been widely reported that the numbers and the proportion of fecal *Bifidobacterium* are increased significantly by the repeated ingestion of FOS.

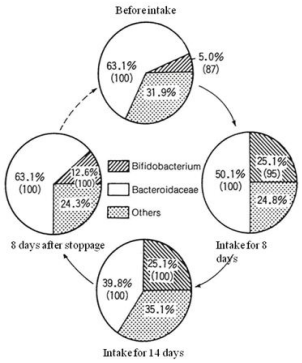

Figure 7: Change of intestinal microbiota by fructooligosaccharide ingestion in the elderly. FOS 8 g/day; n=23; Average age, 73 years

The prebiotic effect of the daily intake of an isotonic solution containing FOS on body weight gain and reduction of diarrhea was evaluated in children in an urban slum in Bangladesh over 6 consecutive months [35]. The daily intake of FOS was not associated neither with the children's growth nor was the number of diarrhea episodes, but a significant reduction in the duration of diarrhea days observed. The mechanism of reducing diarrhea by ingesting FOS is explained as in Figure 8. The daily ingestion of FOS produces many short chain fatty acids, which improve the intestinal environment so that beneficial microbiota such as *Bifidobacterium* and *Lactobacillusincrease* and pathogenic microbiota decrease. The duration of diarrhea is reduced by the improvement of intestinal microflora.

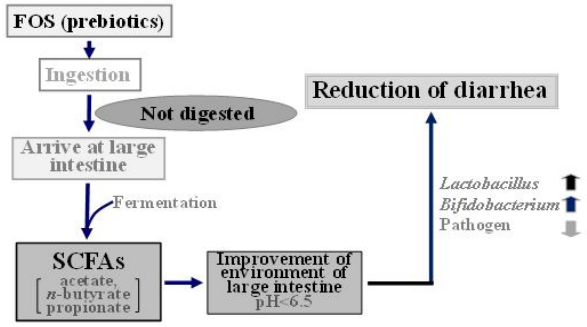

Figure 8: Mechanism of reduction of diarrhea by fructooligosaccharide ingestion.

Resistant oligosaccharides including FOS necessarily improve the composition of intestinal microbiota and bring about health benefits. The proliferation of pathogenic bacteria is suppressed in the intestinal environment, so *Bifidobacterium* and *Lactobacillus* predominate and the incidence of a disease is reduced. The formation of substances during decomposition such as amine, indole, skatole, phenol and sulfide is decreased in the intestinal environment as the number of putrefactive bacteria decrease, and the smell of stools and flatus are also improved [5,10,26-31]. The elderly, in whom the numbers of *Bifidobacterium* have decreased and *Clostridium perfringens* increased, excrete more decomposing substances leading to malodorous stools and flatus discharge. If the elderly repeatedly ingested 3-10 g of FOS per day, the proportion of *Bifidobacterium* would increase and the bad odor would be improved or reduced [5,26-29,33].

Recently, house pets such as dogs and cats increased to live inside houses with humans, where their solid and liquid wastes can cause bad smells in the living space. To improve this, FOS added to pet foods could enhance the quality of life of pet owners [39]. In addition, FOS can be added to the porcine diet to enhance feed efficiency, because domestic animals such as pigs and poultry suffer from osmotic diarrhea when overfed [40,41]. These applications of FOS illustrate the practical use of the prebiotic effect.

Accelerating Defecation of Fructooligosaccharide

FOS is readily fermented by gut microbiota and short chain fatty acids are produced during the fermentation. The short chain fatty acids produce an acidic environment in the lower intestine and accelerate the defecation through stimulating the peristaltic movement of the gastrointestinal tract. There is much evidence that a repeated daily ingestion of 3-15 g of FOS accelerates defecation through increasing stool volume and frequency, normalizing the stool condition and behavior and improving the composition of intestinal microbiota (Figure 9) [41-51]. In the investigations cited, a FOS solution, a lactic acid bacteria beverage containing FOS and processed foods containing FOS, have each been used as test substances.

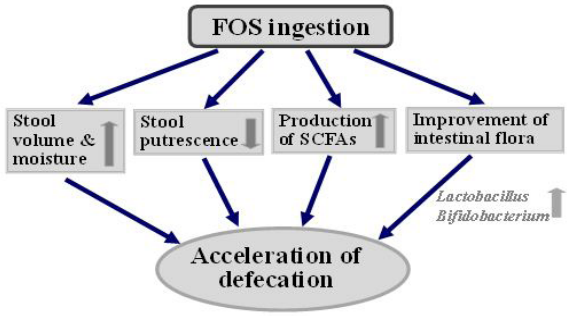

Figure 9: Scheme of accelerating effect of FOS for defecation.

Tokunaga et al. [41] first reported that the repeated ingestion of FOS increased the frequency of defecation in young subjects experiencing light constipation. Healthy students (21 males, 6 females), who ingested 3 g or 5 g of FOS per day for 2 weeks, significantly increased their weekly frequency of defecation. At the same time, the numbers of *Bifidobacterium* increased significantly and their stools became softer and eased defecation. Tominaga et al. [43] also reported that when 3 g of FOS was ingested by young females (18-21 years old, n = 75) once per day for 4 weeks, the fre-

quency of defecation increased significantly in nine subjects whose frequency of defecation was between three and five times per week but did not increase in subjects with a frequency of defecation of less than three or more than five times per week. Overall, FOS ingestion improved defecation in subjects with light constipation. Ohashi et al. [44] also reported that when young females (n = 37) ingested 4.8 g of FOS per day for 2 weeks, the frequency of defecation increased significantly in subjects with light constipation. The ammonia content in the stools also decreased significantly and the numbers of *Bifidobacterium* clearly increased in subjects whose frequency of defecation had improved. Shimoyama et al. [45] reported that elderly patients with heavy constipation, whose frequency of defecation was three to four times per week, showed no acceleration in defecation by ingesting 8 g of FOS per day, but for elderly patients with a frequency of defecation of five to six times per week, defecation was accelerated. In the experiment, the numbers of *Bifidobacterium* and *Lactobacillus increased*, but caused no excess fermentation. Many studies have reported that defecation has been accelerated by FOS ingestion in subjects with light constipation, although no improvement appeared in patients with heavy constipation or in healthy humans with normal defecation [46-51]. In summary, an adequate intake of FOS seems to accelerate defecation in healthy humans with light constipation through the production of short chain fatty acids, and causes an increase in stool volume and moisture and improves the intestinal microflora.

Maximum Permissive Dose For Transitory Laxative Effect of Fructooligosaccharide

Since FOS is not digested by enzymes in the small intestine, an extensive intake of FOS causes essentially laxative effect. Oligosaccharides and sugar alcohols which are resistant to digestion and absorption in the small intestine also certainly cause transitory laxative effect. The mechanism of laxative effect seems to be same as that in lactose intolerance (Figure 10). The excessive ingestion of lactose by a patient with lactose intolerance increases osmotic pressure in the large intestine and thus causes transitory laxative effect.

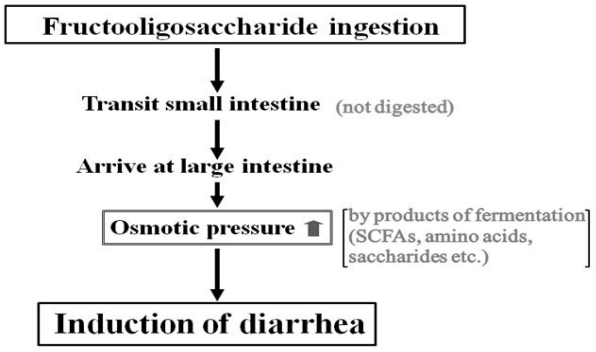

Figure 10: Mechanism of transitory osmotic diarrhea induced by fructooligosaccharide ingestion.

It is essential to know the maximum permissive dose that does not cause laxative effect when developing beverages and processed foods containing FOS. This dose has been determined as 0.3 g FOS per kg of body weight for the adult Japanese male and 0.35 g FOS per kg of body weight for the adult Japanese female [52]. This means that a male with 70 kg of body weight does not suffer from laxative effect after one ingestion of less than 21 g (0.3 ×70 kg = 21 g) of FOS, neither does a female with a 60 kg of body weight after one ingestion of less than 21 g (0.35 ×60 kg = 21 g) of FOS. Table 2 shows the maximum permissive dose for other sugar substitutes which are used in Japan [53,54]. Generally, the maximum permissive dose for transitory laxative effect seems to be lower in males than in females [4-6,46].

Table 2 Maximum permissible dose of sugar substitutes not causing transitory diarrhea

	Sugar substitutes	Maximum permissible dose (g/kg body wt) Male		Female	
Mono-saccharides	Erythritol	0.46		0.68	
	Xylitol	0.37		0.42	
	Sorbitol	0.24	0.15[a]	0.27	0.3[a]
	Mannitol	0.18		0.24	
	D-tagatose	-		0.25	
Di-saccharides	Maltitol	-	0.3[a]	0.30	0.3[a]
	Lactitol	0.25		0.34	
	Palatinit	0.3d		-	
	Lactose	-		0.71	
	Trehalose	-		0.65	
	Cellobiose	-		0.36	
	Lactulose	-		0.32	
	DFAII	0.16		0.22	
Oligo-saccharides	1-Kestose	0.25		0.34	
	Galactosyl-sucrose	-	0.6[b]	0.8	0.6[b]
	4'Galacto-oligosaccharide	0.28[c]		0.14[c]	
	6'Galacto-oligosaccharide	0.3[e]		0.3[e]	
	Xylo-oligosaccharide	0.12[f]		-	
	Fructooligosaccharides	-	0.35 0.3[e]	0.34	0.36 0.4[e]
	Isomalto-oligosaccharides	>1.5[c]		-	
	Soybean-oligosaccharides	0.64[c]		0.96[c]	

Maximum permissive dose are estimated by as follows. a; Koizumi et al., b; Mikuni et al., c; Hata et al., d: Mitsui sugar Co.; e: Yakult Co., Ltd.; f: Suntory Co., Ltd.; No mark: Oku et al.

The maximum permissive dose is changed by the way which resistant oligosaccharide including FOS is eaten [55]. For example, if the amount of FOS causing laxative effect in single ingestion is spread over two or three occasions, no laxative effect occurs. Because FOS is gradually fermented by gut microbiota, the osmotic pressure does not increase rapidly. If ingesting FOS cause laxative effect, its ingestion should be stopped once and then a smaller amount of a half or less should be ingested repeatedly for 1 week or more. As a result, the initial amount of FOS does not cause laxative effect, because the number of gut microbiota which readily utilizes FOS increases and so the osmotic pressure does not increase rapidly. Recovery from laxative effect by adaptation has been investigated particularly by animal experiments using rats [38].

When rats are fed a diet containing 10% FOS or other non digestible oligosaccharides, they suffer from essentially laxative effect immediately after being fed [38]. However, if rats are fed the same diet during 2 weeks or more, they recover from the laxative within 1-2 weeks and the stool shape returns to normal (Figure 11). The metabolism of FOS to short chain fatty acids and carbon dioxide under anaerobic cultivation occurs more rapidly in the cecal content of rats fed a diet containing FOS than that in rats fed a diet without FOS [10]. The spectrum of gut microbiota is changed

by the repeated ingestion of FOS: the number of those microbiota which readily utilizes FOS, increases during the recovery. The number and proportion of *Bifidobacterium* increase during recovery from loose stools. In humans, the repeated ingestion of FOS also leads to resistance to laxative effect. Overall, the maximum permissive dose undoubtedly increases through the repeated ingestion of FOS.

In addition, abdominal symptoms such as thirst, flatus, distension and borborygmus have sometimes been observed because the ingestion of FOS produces gases such as CO_2, H_2 and CH_4 from gut microbiota. However, these symptoms ameliorate during the repeated ingestion of FOS, because *Bifidobacterium*, which produces little gas, gradually proliferates [52]. It seems that the only side effect induced by the extensive ingestion of FOS is transitory loxative effect.

Suitable intake of fructooligosaccharide for health benefits

The amount of FOS to be added to a processed food to show a health benefit or the necessary amount of a food containing FOS depends on the objective of the health benefit. In Japan, the reasonable intake of FOS for an expected health benefit must be established by FoSHU where the valid intake of a particular food is decided. For example, one large intake of FOS cannot reveal the expected effect on the health of the human body through improving the gut microflora: a certain amount of FOS must be ingested repeatedly for a week or more to reveal the effective health benefit.

In the case of beverages containing FOS, as the minimum effective dose (3-4 g/day) based on experimental data is added in one dose, drinking one bottle (or can) per day can improve the composition of gut microbiota and the consistency, color and odor of stools within a few days. The minimum effective dose is less than one-five of the maximum permissive dose for adult males and females. Therefore, the ingestion of less than 5 bottles (or cans) containing 4 g of FOS would not cause laxative effect or abdominal symptoms such as thirst, flatus, distension and borborygmus.

In the case of health benefits as a sweetener for reducing the incidence of dental caries, as FOS cannot prevent dental caries caused by ingesting sucrose, sucrose in food should be replaced by FOS as far as possible. Thus a reasonable intake of FOS as a sweetener is not relevant in food for reducing dental caries. Furthermore, as the available energy of FOS (2 kcal/g, 8.368 kJ/g) is half that of sucrose, using FOS as a substitute for sucrose can decrease energy intake. However, the extensive intake of FOS should be avoided if anyone is anxious about obesity, because the increases in energy intake depend on the amount of FOS intake. A reasonable intake of FOS as a sweetener with low energy is also not relevant in food for reducing energy intake. In addition, as FOS does not increase blood glucose and insulin levels, patients with diabetes mellitus can use FOS as an alternative sweetener to sucrose but an extensive intake of FOS cannot improve the symptom of diabetes. So as an alternative sweetener to sucrose, a reasonable intake of FOS does not exist.

Summary of health benefits of fructooligosaccharide

As mentioned above, FOS has various physiological functions and expresses beneficial health effects for the body. The health benefits of FOS are summarized as follows;

1) Sweetener with low available energy [12,13,56].

As the available energy is a half of sucrose, 2 kcal/g, it can use as a low energy bulking sweetener. But, the sweetness of FOS is about 30% of sucrose.

2) No stimulation of insulin secretion [3,13,56,57].

As FOS is not hydrolyzed by glucosidases such as α-amylase and small intestinal disaccharidase, the ingestion of FOS does not increase blood glucose, fructose and insulin levels. [3,13,56,57]. The patients with diabetes mellitus can use FOS as a sweetener without insulin secretion.

3) Improvement of intestinal microflora (prebiotics) [5,26-36].

FOS is readily fermented by gut microbiota and produced spontaneously short chain fatty acids improving the environment in gastrointestinal tract. As a result, the repeated ingestion of FOS necessarily improves the composition of intestinal microbiota and brings about health benefits.

4) Acceleration of immunological functions [37,58-60].

The immunological function is accelerated in the environment of gastrointestinal tract of which total numbers and proportions of pathogenic microbiota decrease and the beneficial microbiota such as *Bifidobacterium* and *Lactobacillus* steadily increase in numbers and proportion.

5) Stimulation of intestinal minerals absorption [61-66].

Short chain fatty acids produced from FOS by gut microbiota cause the acidic condition which increases the solubility of minerals. In addition, the absorptive area of gastrointestinal tract is expanded by ingesting FOS. Therefore, the absorption of minerals such as calcium, magnesium and iron increases.

6) Maintaining the physiological function of the gastrointestinal tract [67,68].

As the synthetic diet without nondigestible carbohydrates such as dietary fiber and FOS causes an atrophy of villi in the small intestine, the function of digestion and absorption declines. FOS which is resistant prevents the atrophy of small intestine and maintains normally the function of the gastrointestinal tract.

7) No induction of dental caries [69].

As FOS is not utilized by mutans streptococci (bacteria of dental caries), oral pH does not decline and water-insoluble glucan is not produced. Therefore, if FOS is used instead of sucrose, dental caries is not caused.

Conclusion and Perspectives

In order to gain the expected health benefit of resistant sugar substitutes including FOS, the following points should be considered.

1) Eating a large amount of resistant sugar substitute once should be avoided (Ingesting a large amount will cause transitory laxative effect and abdominal symptoms).

2) Eating a combination of foods containing a sugar substitute with similar health benefits should be avoided (If the content of sugar substitute in a food is under the maximum permissive dose, the combination of some foods may exceed the maximum permissive dose).

3) The labeling on the food package should be carefully read (The optimum intake per day or in one dose is mentioned on the label. Increasing the intake of sugar substitute does not lead to better health).

4) The sugar substitute used should correspond to the required physiological function (The amounts of sugar substitute differ according to their use as a prebiotic or as a sweetener). A reasonable intake of nondigestible or resistant sugar substitutes including FOS should contribute to promoting health and preventing life-related disease.

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