Research Article

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The Controversy: Whether Sucralose Could Increase Blood Glucose in The Body?

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ABSTRACT

Sucralose is the most used artificial sweetener around the world, accounted for 30% of the global low-calorie sweetener market in 2016. According to the inspection of 19915 pre-packaged foods in Hong Kong, sucralose is the most used non-nutritive sweetener, followed by acesulfame. In addition to the food industry, sucralose can also be used as one kind of subsidiary materials for correcting taste in suspension agent, oral liquid, tablets, and granules, which could cover up the bitter taste of medicines such as aspirin or traditional Chinese medicine compound. The Food and Drug Administration (FDA) had approved the use of sucralose, but whether sucralose intake has effect on blood glucose is not clarified clearly. For this purpose, we collected and summarized the clinical studies to evaluate the effect of sucralose intake on blood glucose since 1996 from PubMed database, hope it may provide some evidence for sucralose applications in food excipient or drug sweet excipient.

Keywords: Sucralose, sweetener, blood glucose, sweet excipient

INTRODUCTION

Sucralose is a kind of sucrose derivative made from sucrose through acylation and chlorination, commonly known as sucralose. Sucralose was developed firstly by Tate & Lyle and the University of London in 1970s [1]. In 1998, the FDA expanded the permissible use of sucralose to include its use as a conventional sweetener in all kinds of food and beverages [2,3]. In addition, the Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives conduct systematic and meticulous safety assessments on sucralose as a food additive [4]. The chemical name of sucralose is 4,1',6'-trichloro-4,1',6'-trideoxy-galacto-sucrose, the molecular formula is $C_{12}H_{19}Cl_3O_8$, and the molecular weight is 397.64. Characteristically, sucralose is 600 times the sweetness sucrose, has a high melting point of 125 °C, and exhibits high stability to changes in pH, light, heat, etc. As one kind of food additives, the ADI of sucralose is 15 mg/kg/d of body weight according to the provisions derived from three agencies, including the Joint Expert Committee on Food Additives (JECFA), European Food Safety Agency (EFSA), as well as National Administration of Drugs, Foods and Medical Devices (ANMAT) [5]. Besides, FDA has stipulated the ADI of sucralose is 5mg/kg [6]. After oral administration of 1 mg/kg of sucralose, the proportion of sucralose excreted through feces and urine is 78.3% and 14.5%, respectively. And its main excretion in the feces is prototype metabolite, while the main forms present in the urine are sucralose and a small amount of sucralose glucosidic acid [7]. The peak time of plasma is 1-3 hours, and the half-life is 13 hours [8]. 5% to 20% sucralose will really enter the blood, but whether sucralose intake has effect on blood glucose is controversial. For this purpose, we collected and summarized the relative clinical studies since 1996 from PubMed database, to discuss the effect of sucralose intake on blood glucose.

METHODS

In order to evaluate the effect of sucralose intake on blood glucose clinically, we searched the keywords "subclause", "sweeters", "non-nutritive sweeters", "splenda", "die soda", "die drink", "die coverage" in the PubMed database, filtered

the retrieved results by title, abstract and subject headings according to the following criteria: (1) The articles belonged to randomized clinical trial (excluding Letter/Comment/ Technical development, etc.); (2) The research object was human beings; (3) The object of the study was to study the effect of sucralose on blood glucose.

RESULTS

The effect of single sucralose intake on blood glucose

The collected data demonstrated that the maximum daily intake dose of sucralose was 6000mg, and the minimum daily intake dose of sucralose was 12mg. Among the total of 20 articles, 4 articles reported that sucralose could result in blood glucose to rise; interestingly, the daily intake dose of sucralose in the 4 articles was 48mg, the dosage form was solution and the administration was oral. In addition, there were two articles that reported that subjects with elevated blood glucose were accompanied by obesity. The evidence suggested that there was no dose effect on the effect of single intake of sucralose on blood glucose (Table 1).

Table 1: The summarized data of the effect of single sucralose intake on blood glucose

Whether it affects blood sugar	ADI	Dosage/ day	Whether in combination with other sugars	Dosage form	Administration	Whether Diabetes	Reference
None	333.3%	1000mg	None	Capsule	Oral	Type 1 diabetes	[9]
	333.3%	1000mg	None	Capsule	Oral	Type 2 diabetes	
	26.7%	80mg	None	Solution	Gavage	None	[10]
	266.7%	800mg	None	Solution	Gavage	None	
	15.3%	46mg	26mg acesulfame K	Solution	Oral	None	[11]
	320.0%	960mg	None	Solution	Duodenum	None	[12]
	Not provided	50mL	None	Solution	Oral	None	[13]
	2000.0%	6000mg	None	Solution	Oral	None	[14]
	20.7%	62mg	None	Solution	Duodenum	None	[15]
	20.0%	60mg	None	Solution	Oral	None	[16]
	15.3%	46mg	26mg acesulfame K	Solution	Oral	None	[17]
	15.3%	46mg	26mg acesulfame K	Solution	Oral	Type 1 diabetes	
	15.3%	46mg	26mg acesulfame K	Solution	Oral	Type 2 diabetes	
	17.3%	52mg	None	Solution	Oral	None	[18]
	53.0%	159mg	None	Solution	Oral	None	[19]
	8.0%	24mg	None	Solution	Oral	None	[20]
	8.0%	24mg	None	Solution	Oral	Type 2 diabetes	
	22.7%	68mg	None	Solution	Oral	None	[21]
	56.7%	170mg	None	Solution	Oral	None	
	83.3%	250mg	None	Solution	Oral	None	
	22.7%	68mg	41mg acesulfame K	Solution	Oral	None	
	6.0%	18mg	18mg acesulfame K +57mg Aspartame	Solution	Oral	None	
	95.3%	286.3mg	None	Solution	Duodenum	None	[22]
	22.7%	68mg	None	Solution	Oral	None	[23]
	16.0%	48mg	None	Solution	Oral	None	
	11.7%	35mg	None	Solution	Oral	None	[24]
	66.7%	200mg	None	Solution	Oral	None	[25]
	110.0%	330mg	None	Solution	Oral	None	
	40.0%	120mg	None	Solution	Oral	None	[26]
Blood glucose elevating	16.0%	48mg	50g saccharose+50g Isomaltose	Solution	Oral	None	
	16.0%	48mg	None	Solution	Oral	Obesity	[27]
	16.0%	48mg	None	Solution	Oral	None	[28]
	16.0%	48mg	None	Solution	Oral	Obesity	

The effect of long-term sucralose intake on blood glucose

For understanding the effect of long-term sucralose intake on blood glucose, a total of 15 relevant articles were collected. We found that the maximum daily intake and minimum daily intake of sucralose were 1000 mg and 36 mg, while the maximum and minimum administration times were 13 weeks and 1 week. In the total of 17 relevant articles, there were 6 articles reported that long-term sucralose intake will affect the blood glucose; and in the 6 articles, there were 4 articles reported that sucralose in combination with other sugars including saccharose, carbohydrate, Maltodextrin, or glucose, this maybe the main reason why the blood glucose increases in the article (Table 2).

DISCUSSION

In the 35 clinical studies, there were 17 articles reported that the single sucralose intake had no effect on blood glucose (Table 1), and 11 articles reported that the long-term sucralose intake had no effect on blood glucose (Table 2). 7 articles have reported that sucralose caused blood sugar to elevate, with data from three single intake experiments and four long-term intake experiments, respectively. We analyzed and summarized the potential factors that may contribute to elevating blood glucose from sucralose intake.

1. Sucralose is used together with other kinds of sugars.

The study has found that healthy people drank sucralose+sucrose+isomaltose at single time led to an increase in blood glucose at 30 min of glucose tolerance, while sucralose intake alone has no effect on blood glucose [26]. Suez J, et al demonstrated that healthy people dieted the combined aqueous solution of sucralose and glucose for 17 days, resulting in increased blood sugar and intestinal flora imbalance [42]. Malbert CH, et al. provided evidence that obese miniature pigs fed with the combination of sucralose and acesulfame K for 3 months, abdominal fat increased by 20% and insulin clearance decreased by 40% [43]. The data of Risdon S, et al showed that after drinking the aqueous solution of acesulfame potassium and sucralose in the range of ADI for 10 weeks, healthy rats had obvious vascular endothelial dysfunction [44]. Sánchez-Tapia M, et al. demonstrated that metabolic endotoxemia rats fed with sucralose and high-fat diet for 4 months led to an increase in the abundance of Bacillus fragilis, a decrease in the abundance of obliterans, and an increase in pro-inflammatory cytokines, glucose intolerance, fatty acid oxidation and ketone body [45]. These evidences demonstrated that the combination of sucralose and various sugars can cause higher levels of blood sugar and result in various side effects.

2. Combination of sucralose and carbohydrate

Dalenberg JR, et al. demonstrated that the healthy people

Table 2: The summarized data of the effect of long-term sucralose intake on blood glucose.

Whether it affects blood sugar	Dosage/day	Whether in combination with other sugars	Dosage form	Duration	Whether Diabetes	Reference
None	125-500mg	None	Solution	13 weeks	None	[8]
	No data	None	Biscuit	4 weeks	Type 2 diabetes	[29]
	667mg	None	Capsule	13 weeks	Type 2 diabetes	[30]
	1000mg	None	Capsule	12 weeks	None	[31]
	36mg	None	Solution	2 weeks	None	[32]
	200mg	None	Capsule	4 weeks	None	[33]
	156mg	11.8g glucose	Solution	2 weeks	None	[34]
	136mg	None	Solution	2 weeks	None	[35]
	160mg	None	Solution	12 weeks	None	[36]
	780mg	None	Capsule	1 weeks	None	[37]
	66mg	None	Solution	4 weeks	None	[38]
Blood glucose elevating	60mg	30.38g saccharose	Solution	2 weeks	None	[39]
	60mg	31.83g carbohydrate	Solution	2 weeks	None	
	48mg	0.39g Maltodextrin+12.5g glucose	Solution	10 weeks	None	[40]
	96mg	None	Solution	10 weeks	None	
	48mg	None	Solution	10 weeks	None	[41]
	103mg	5.89g glucose	Solution	2 weeks	None	[42]

drank a combination of sucralose and carbohydrates for 2 weeks, resulting in impaired glucose metabolism and reduced sensitivity to sweetness of central nervous system, but there was no the similar phenomenon in people who drink sucralose only or carbohydrates only [39]. Bueno-Hernández N, et al. provided the evidence that healthy people diet on the combination drink of sucralose+carbohydrate+glucose for 10 weeks, resulting in insulin increase [40]. These evidences suggest that sucralose combined with carbohydrates may result in the increase of blood sugar, it is recommended to reduce food or drink containing sucralose when dinner.

3. Sucralose+TV/game/audio

The result of Bellissimo N, et al. demonstrated that healthy children can increase their food intake equivalent to 228 kcal by drinking an aqueous solution containing 1.0 g/kg of sucralose at one time while eating lunch and watching TV [46]. Gheller B, et al. observed that the obese children play video games after taking 150mg of sucralose before meals, resulting in an increase in subjective appetite, subjective mood and cumulative food intake [47].

4. Sucralose stimulates the sweet taste reward of the mouth.

Sucralose is a powerful taste receptor agonist, the study demonstrated that 39 μM sucralose was enough to activate sweet receptor signal [49], while glucose needs to be activated at very high concentration (>300mM) [50]. Compared with fructose and sucrose, sucralose-induced hypothalamic blood oxygen level-dependent imaging reaction was the smallest and the shortest in duration, which was like that induced by boiled water, indicating that sucralose may not have similar satiety effect on the brain as natural sugar [51]. To avoid the sweet oral reaction, sucralose can be considered to be administered in the form of capsule, inasmuch as many articles had reported that there is no increase in blood glucose was observed in all clinical studies of taking sucralose in capsule [9,30-31,33,37].

CONCLUSION

The effect of sucralose on blood glucose is contradictory. Especially, the results of Suez J, et al. overturned the previous assertion that sucralose is inert in human body, they demonstrated that sucralose could cause blood glucose to rise by affecting intestinal microorganisms [42]. However, we cannot ignore the four preconditions involved in this study: (1) the participants were given a combination of sucralose and glucose, and no sucralose group was set in this study; (2) There is no standard diet, which just controls the lower limit of daily calorie intake rather than the upper limit in the study; (3) Sucralose did not cause the increase of blood glucose in people with low glucose sensitivity. For example, the article title "Personalized" emphasized individual differences. (4) The glucose tolerance test is too frequent (3.1 times per week on average), which may aggravate the stimulation of islet function.

In conclusion, the effect of sucralose on blood glucose and intestinal flora is objective. The extent of its effect depends not only on the dose and the number of days of continuous intake, but also on whether it is combined with other sugars or carbohydrate, whether a standard diet is set to control the upper limit of daily calories, whether it distinguishes the sugar-sensitive population, the number of glucose tolerance tests, and whether it avoids oral sweet reaction (using capsule instead of solution). Controlling these variables well is beneficial to the safe application of medicine containing sucralose. If necessary, sucralose consumption can be guided by the flora data obtained in the feces derived from patients.

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CONFLICT OF INTERESTS

There is no conflict of interest in this article.

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