DE GRUYTER OPEN

© **2017** ILEX PUBLISHING HOUSE, Bucharest, Roumania
http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **24**(2):127-135
doi: 10.1515/rjdnmd-2017-0017

THE EFFECT OF CHEWING A SUGAR-FREE GUM AFTER OATMEAL ON THE POSTPRANDIAL GLYCAEMIA – A CROSS-OVER STUDY

Lea Vuletic [1,✉], ***Marija Klaic*** [2], ***Stjepan Spalj*** [3], ***Kristina Peros*** [4]

[1] Department of Physiology, School of Dental Medicine, University of Zagreb, Zagreb, Croatia
[2] Student of the School of Dental Medicine, University of Zagreb, Zagreb, Croatia
[3] Department of Orthodontics, School of Medicine, University of Rijeka, Rijeka, Croatia
[4] Department of Pharmacology, School of Dental Medicine, University of Zagreb, Zagreb, Croatia

received: April 25, 2017 *accepted*: May 31, 2017
available online: June 15, 2017

Abstract

Background and Aims: *Gum chewing after a meal stimulates salivation and may affect the motility of the gastrointestinal tract and the release of hormones through neural mechanisms. This study was conducted to assess if chewing a sugar-free gum for 20 min following a meal, as recommended for dental caries prevention, influences the postprandial blood glucose levels in a period of one hour.* ***Materials and Methods:*** *For each of 18 participants blood glucose profile was made by measuring capillary glucose concentration in 10-min intervals within one hour following: a) chewing a sugar-free gum, b) the consumption of an oatmeal, c) chewing a sugar-free gum after the consumption of an oatmeal.* ***Results:*** *No statistically significant differences were found in the glycaemic response following complex carbohydrate ingestion when a gum was chewed after a meal.* ***Conclusions:*** *The possible influence of gum chewing on the postprandial gastrointestinal and metabolic ongoings was not reflected in the postprandial glycaemic response under the conditions of this study. A more comprehensive study which would include more variables related to vagal efferent activity, digestion and metabolism would be needed to assess if chewing sugar-free gums to exploit their caries-protective potential can influence metabolic adaptability to nutritional challenges.*

key words: *dietary carbohydrate metabolism; high carbohydrate meal; mastication; postprandial glucose response; stimulated saliva; sugar-free chewing gums*

Background and Aims

It is widely accepted that chewing sugar-free gums is beneficial to oral hygiene and, consequently, to the preservation of oral health. A recommendation to chew a gum for at least 20 min after eating or drinking which can be found on the covering of many commercial sugar-free gums is endorsed by studies confirming that such a usage can reduce the incidence of dental caries [1,2]. The principal mechanism by which all sugar-free gums exert their beneficial oral

✉ Salata 3, 10 000 Zagreb, Croatia, Phone number: +385-1-4590243
corresponding author e-mail: vuletic@sfzg.hr

effects is by stimulating the secretion of saliva which then rinses the oral cavity of food debris. Due to a significantly higher concentration of hydrogen carbonate ions in stimulated saliva, gum chewing also raises the oral *p*H and enhances the neutralisation of plaque acids thus favouring local conditions favourable for the remineralisation of hard dental tissues [3].

Saliva also participates in the digestive function of the mouth. Its alimentary functions, primarily of stimulated saliva, include lubrication which facilitates mastication and swallowing, bolus formation, and different roles in taste recognition. Saliva contains digestive enzymes, lingual lipase and, particularly, salivary amylase (SA). SA comprises about 30% of the total protein content of parotid saliva [4]. Under stimulated conditions the contribution of parotid saliva to the total volume of mixed saliva increases from approximately 20% to more than 50% [5]. The nutritional advantage provided by the breakdown of starch by SA has not been established [6]. Its enzymatic activity is generally considered limited by a relatively short time of processing the food in the mouth before swallowing and, in the gastric phase of digestion, by a low pH of the gastric juice [7]. However, it has been shown that thorough chewing of food affects the digestibility and the glycaemic response to different carbohydrate foods [8-10]. Proposed mechanisms underlying such effects of mastication include the reduction in particle size which could enhance the delivery of food from the stomach to the small intestine; the increase in the surface area of the ingested food and thus the increase in the surface for pancreatic enzymes to act upon; the enhancement of salivation which could increase carbohydrate digestion rate in the mouth and in the stomach; and the potentiation of early-phase insulin secretion. There are reports which suggest that the levels of SA could be related with preabsorptive (cephalic) phase insulin release and glycaemic homeostasis following starch ingestion in adults [11].

This study was conducted in order to assess whether chewing a sugar-free gum for 20 min following a meal influences the postprandial blood glucose levels in a period of one hour. Chewing a flavoured (minted) sugar-free gum significantly increases the amount of stimulated saliva which enters the stomach. At the same time, masticatory movements and orosensory stimulation related to gum chewing could modify postprandial digestive processes by affecting the motility of the gastrointestinal tract and by influencing the release of hormones through neural mechanisms [10,12-15]. The finding of the presumed influence would indicate that chewing sugar-free gums to exploit their caries-protective potential is accompanied by systemic effects on the carbohydrate/glucose metabolism.

Materials and Methods

The study was planned as a randomised cross-over trial in which each participant would undergo three different protocols at three separate visits as shown in Table 1.

Minimal sample size of 14 participants was calculated using the data from two preliminary sets of measurements: average difference of 0.35 units between the oatmeal treatment and the oatmeal+chewing gum treatment in each time point in which glucose measurements were performed (the range was 0.2-0.5); within-subject standard deviation of 0.3; statistical power of 0.8 and a significance level of 0.05 for a two-sided test. Calculations were made using an online calculator http://hedwig.mgh.harvard.edu/sample_size/size.html (accessed 5 June 2015).

A total of 107 undergraduate students of the School of Dental Medicine, University of Zagreb

were presented with the study protocol and invited to participate. Exclusion criteria included suffering from any disease and/or usage of medicines, food allergy and/or food intolerance, wearing fixed orthodontic appliances and smoking. Because the total number of volunteers who met inclusion criteria was only 18 (15 females and 3 males), they were all included in the study sample. Students were aged 20-22 years (median 21, interquartile range 20-21) and were within the normal range of body weight for their height (body mass index (BMI) was 21.9±1.9 kg/m^2).

Table 1. The scheme of the study design

Protocol	Measurement of baseline (fasting) blood glucose concentration	Meal consumption	A 1h monitoring period: measurement of blood glucose concentration in 10-min intervals within one hour	
Chewing gum	+	-	Chewing a sugar-free gum during the first 20 min of the 1h monitoring period	+
Oatmeal	+	+		-
Oatmeal + chewing gum	+	+		+

The order of the protocols for each participant was randomised using Microsoft Office Excel's RAND function. The three visits were scheduled within a period of three to ten days depending on the student's availability in the morning hours. Measurements were performed at the School of Dental Medicine beginning in the period between 8.00 and 8.30 am. The participants were requested to fast and to sleep over the night before measurements. They were also encouraged to keep physical activity to a minimum on the morning before testing. Physical activity was restricted during the 1h monitoring period and unnecessary conversation was avoided.

The meal the participants were requested to consume was 20 g of finely crunched oat grains (SPAR Natur*pur Bio-Hafermark, 250 g, Salzburg, Austria). The nutrient composition of the dietary product is given in Table 2. The oats were mixed with 80 mL of water for 2 min and the participants were instructed to eat (basically only swallow) the meal within 2-3 min. The cup was subsequently rinsed with 20 mL of water and the participants rinsed their mouth with it and swallowed it.

Table 2. The nutrient composition of the meal as stated on the product label

100 g of the SPAR Natur*pur Bio-Hafermark contains averagely:	
Energy	1591 kJ/ 377 kcal
Fat	7.0 g
thereof saturated fatty acids	1.3 g
Carbohydrate	63 g
thereof sugar	0.8 g
Fiber	5.4 g
Protein	13 g
Salt	0.02 g
Bread exchange units	5.3 BE

Sugar-free chewing gums used in the study were Wrigley's Orbit Spearmint sticks (Wrigley France S.N.C., Biesheim, France). No instructions were given to the participants with regard to gum chewing; they chewed at their individual (preferred) pace for 20 min.

Blood glucose was measured using Contour XT glucometers and Contour Next test strips (Bayer Consumer Care AG, Basel, Switzerland). The participants washed their hands with soap

and water prior to the fasting glucose measurement. Fingertips were additionally cleaned with an alcohol-based hand sanitiser (Plivasept blue, Pliva, Zagreb, Croatia) prior to every prick. The glucose measurements were performed on the first drop of blood as suggested by the manufacturer's instructions. However, 110 glucose measurements on 15 participants were performed on both the first and the second drop of blood (if the second drop could be obtained by using only a light pressure upon the finger) in order to test for possible differences. The fingertip was wiped off with dry cotton after testing the first drop. The glucometers were calibrated at the beginning of the study and several times during the study.

The study was approved by the Ethics Committee of the School of Dental Medicine, University of Zagreb, Croatia. Written informed consent was obtained from all participants prior to their inclusion in the study.

Statistical analysis

The Shapiro-Wilk test was used to test the assumption of normality, and Levene test was used to test for homogeneity of variance.

The intraclass correlation coefficient (ICC) was used to assess the consistency or reproducibility of the glucose concentration measured in the first and the second drop of blood obtained by the same prick. Paired samples t-test was used to test differences in the glucose concentration between the two blood drops.

One-way ANOVA with the Sidak post-hoc test was used to compare the chewing gum group (CGG), the oatmeal group (OG) and the oatmeal+chewing gum group (O+CGG) at each time point within the period of one hour.

The participants were also divided into two groups depending on the order of the visits which was randomly allocated for each participant. The first group was comprised of those to whom glucose measurements following oatmeal (without gum chewing) were performed prior to the glucose measurements when a gum was chewed after oatmeal. A mixed-design ANOVA was used to determine whether any change in the dependent variable was the result of the interaction between two independent variables, the visits order (the between-subjects factor) and time (the within-subjects factor).

Repeated measures ANOVA with the Sidak post-hoc test was used to compare glucose concentration between time points for each of the three groups.

Eta squared (η^2) was used to estimate the size of the effect, that is the share of the total variability of the dependent variable explained by the factor tested with Cohen criteria used for interpretation: 0.02-0.13 = small; 0.13-0.26 = medium; >0.26 = large effect size [16].

Because we used the same amount of oatmeal for all participants, Pearson's correlation was used to test the association between the glucose concentrations at each time point with BMI.

The data were analysed using statistical software IBM SPSS 22 (IBM Corp., Armonk, NY, USA) with significance preset at $\alpha<0.05$ for a two-sided test.

Results

Excellent reproducibility was demonstrated in repeated measurements of glucose concentration, ICC=0.96; 95% CI: 0.81-0.99, $p<0.001$. The difference in the glucose concentration measured in the first and the second drop of blood obtained by the same prick was small (0.14±0.15 mmol/L) but statistically significant as revealed by paired samples t-test. The results suggest a higher glucose concentration in the second drop in comparison

with the first, 5.63±0.81 mmol/L vs. 5.49±0.79 mmol/L, respectively, P<0.001.

The results of one-way ANOVA showed statistically significant differences between the three groups at time points t20-t60 (Table 3). The effect size was large for t20-t50 (0.275-0.472), the largest being at t30, and small at t60. The Sidak post-hoc test revealed that the difference is significant between the CGG and OG, and between CGG and O+CGG.

Table 3. Dynamics of changes in glucose concentrations during a one hour observation period for the study groups

	Glucose concentration (mmol/L)							
	Chewing gum group (N=18)		Oatmeal group (N=18)		Oatmeal + chewing gum group (N=18)			
Time point	Mean	SD	Mean	SD	Mean	SD	P	η^2
t0	5.02	0.37	4.98	0.46	5.06	0.43	0.86	0.006
t10	5.02	0.34	5.22	0.47	5.36	0.63	0.12	0.079
t20	4.94	0.33	5.79	0.64	5.87	0.90	<0.001*	0.297
t30	4.80	0.27	5.92	0.70	6.14	0.81	<0.001*	0.472
t40	4.83	0.33	5.77	0.59	5.78	0.75	<0.001*	0.380
t50	4.78	0.31	5.53	0.65	5.42	0.63	<0.001*	0.275
t60	4.71	0.31	5.10	0.59	5.07	0.51	0.03*	0.125

t0 = time of baseline glucose measurement; t10-t60 = time points separating 10-minute intervals within a 1h monitoring period in which glucose measurements were performed; N = sample size; SD = standard deviation. * statistically significant for one-way ANOVA, P<0.05; η^2 = measure of effect size for group mean differences.

The results of a mixed type ANOVA suggested a statistically significant interaction between the visits order and time on the change of glucose concentration (P<0.001) with a medium effect size (η^2=0.247).

The results of repeated measures ANOVA showed that the difference in the concentration of glucose compared to baseline level (t0) was significant from t20 to t60 for the OG, and from t20 to t50 for the O+CGG (P<0.05) suggesting a faster return to baseline level for the O+CGG. A steeper return of glucose concentration to baseline levels for the O+CGG compared to OG after reaching a maximum at t30 was further seen in that the mean glucose concentration at t30 was statistically significantly different from the glucose concentration at t40 as well as at t50 and t60 (P<0.05) for the O+CGG. On the other hand, for the OG, a statistically significant difference between glucose level at t30 and subsequent time points was not reached until t60. In addition, the difference between t10 and t40 was significant for the OG but not for the O+CGG. The effect size of influence of time points on glucose level was large for both the OG and O+CGG (η^2=0.440 and 0.478, respectively; P<0.001).

Pearson's correlation revealed no significant association between the glucose concentrations at each time point with BMI.

Discussion

The aim of this study was to assess whether chewing a sugar-free gum for 20 min following a meal rich in complex carbohydrates influences postprandial levels of blood glucose. Therefore, the study was designed in a way as to reduce the time of the oral phase of feeding and to minimise the mechanical and gustatory stimulation of salivation during eating. Oats were used as a test meal because such a soft, mushy meal requires no chewing and is essentially flavourless. By avoiding food which needs to be chewed prior to being swallowed we reduced the time of the oral phase of feeding, avoided the influence of the particle size on digestion (i.e. assured a constant and uniform particle size for all participants throughout the whole study course) and

minimised the mechanical stimulation of salivation during eating. In this way we tried to isolate and assess the influence of postprandial gum chewing on the gastrointestinal (digestive and absorptive) and metabolic processes which could, presumably, be reflected in the postprandial levels of blood glucose. However, no significant difference was found in the pattern of the postprandial glucose concentration changes during a 1h monitoring period when a gum was chewed after oatmeal.

Because we reduced the oral phase of feeding, the majority of SA was secreted as a response to postprandial gum chewing. Therefore, a possible hydrolysis of dietary starch by SA took place predominantly in the stomach and/or in the small intestine. However, the postprandial blood glucose changes in the O+CGG in relation to OG do not suggest a significant influence of the SA on the rate of carbohydrate digestion prior to their exposure to the pancreatic juice. Possible explanations include unfavourable relation between the amount of stimulated saliva and the size of the test meal and inactivation of the SA by the gastric acid. Even though stimulated saliva is rich(er) in hydrogen carbonate ions, their amount could be insufficient to counteract a pH drop caused by gastric acid secretion to the extent which could allow/prolong enzymatic activity of SA in the stomach. The gastric environment is simultaneously influenced by the properties of ingested food including its consistency, physical and chemical structure, buffering capacity, starch digestibility and the presence of amylase inhibitors [17-20]. Perhaps the properties of our test meal could not sufficiently protect SA from inactivation by the acidic gastric environment. Its enzymatic activity in the stomach could be additionally attenuated if gum chewing simultaneously stimulated vagally mediated gastric acid secretion [21].

One of the reasons why we used oatmeal was to avoid the influence of chewing on the size of food particles. Chewing is generally regarded as a highly subjective process that varies with individual [22] and, as already mentioned, thorough chewing of food may affect digestibility and the glycaemic response to different carbohydrate foods [8-10]. We used oats in the form of a bran, crunched into very small particles. Because it has been shown that gastric emptying of smaller food particles is faster [23], a shorter gastric transit time would also leave less time for the pre-intestinal enzymatic breakdown of starch by SA. On the other hand, it could enable the pass of a greater amount of SA through the stomach into the duodenum without inactivation especially for the O+CGG. Possible explanations why this was not followed by a more pronounced blood glucose rise in the early postprandial period when compared to the OG include both preabsorptive factors as well as postabsorptive mechanisms that regulate glucose uptake and hepatic production and, in this way, control its blood level. Perhaps, the fraction of the active SA that reached the duodenum and jejunum was nonetheless insufficient to cause any significant influence on the postprandial blood glucose level. On the other hand, the remaining activity of SA in the duodenum could have been concealed by the amylolytic digestion by pancreatic enzymes. The results of an in vitro study by Woolnough et al. [22] suggest that the initiation of simulated intestinal digestion rapidly overwhelms any effect of saliva on the digestion of starch.

Little is known about the metabolic impact of gum chewing. It has been shown that gum chewing may increase fasting and postprandial energy expenditure without altering blood glucose [24]. We found no reports on the influence of postprandial gum chewing on the

insulinaemic responses or the secretion of other endocrine factors closely linked to the function of the digestive tract. The results of certain studies assessing the influence of orosensory stimulation on endocrine and metabolic responses suggest that the phase of oral sensory stimulation by food may be followed by an increase in plasma insulin with or without affecting the level of blood glucose [10,15,25-27]. In addition, sham feeding has been shown to improve glucose tolerance in normal subjects without alteration in insulin secretion [28,29]. Postprandial gum chewing, without supplying the gastrointestinal tract with additional nutrients, sustains masticatory movements and orosensory stimulation. It is possible that this could modify the "regular" postprandial neural and endocrine regulation of the gastrointestinal motility and secretion, and the secretion of pancreatic metabolic hormones. However, this cephalic response to gum chewing (the extent of vagal activation) could be different between people who never or rarely chew gums, and those who chew gums regularly, on a daily basis, and who have created an "experience" of using a sweet stimulus which is not associated with (additional) caloric load [30]. It is also possible that the initial characteristics and magnitude of the modulatory effect might change during the 20 min period of gum chewing because factors related to the gastric and/or intestinal phase of digestion might inhibit or override the cephalic impulses provoked by gum chewing [31]. In addition, attention should be payed to recent suggestions that artificial low-energy sweeteners may precipitate metabolic derangements in susceptible individuals [32].

The principal drawback of the present study is that we could not simultaneously monitor different variables related to glucose homeostasis (e.g. the secretion of pancreatic and gut peptides) and, in this way, gain a more complete insight into the influence of postprandial gum chewing on the (early) postprandial gastrointestinal and metabolic ongoings. Analysis of participants' stimulated saliva would have also provided valuable additional information to the present results. Exposure of oatmeal used in this study to human saliva under in vitro conditions could have indicated the susceptibility of its carbohydrates to the digestion by SA.

Conclusions

In conclusion, possible non-oral (metabolic) outcomes of chewing sugar-free gums after a meal were not revealed under the conditions of our study. Further studies assessing the effects of gum chewing on the metabolic adaptability to nutritional challenges should include more variables related to vagal efferent activity, digestion and metabolism in order to gain a more complete view on these processes.

Acknowledgements & Duality of interest. We thank the students of the School of Dental Medicine, University of Zagreb for participating in this survey. The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We thank the Croatian company MEDiLAB d.o.o. for supporting the study by donating Bayer's products for glucose measurement. The authors report no conflicts of interest.

REFERENCES

1. **Beiswanger BB, Boneta AE, Mau MS, Katz BP, Proskin HM, Stookey GK**. The effect of chewing sugar-free gum after meals on clinical caries incidence. *J Am Dent Assoc* 129: 1623-1626, 1998.

2. Szöke J, Bánóczy J, Proskin HM. Effect of after-meal sucrose-free gum-chewing on clinical caries. *J Dent Res* 80: 1725-1729, 2001.

3. Dawes C, Kubieniec K. The effects of prolonged gum chewing on salivary flow rate and composition. *Arch Oral Biol* 49: 665-669, 2004.

4. Dodds MWJ, Johnson DA, Yeh CK. Health benefits of saliva: a review. *J Dent* 33: 223-233, 2005.

5. Rohleder N, Nater UM. Determinants of salivary alpha-amylase in humans and methodological considerations. *Psychoneuroendocrinology* 34: 469-485, 2009.

6. Mandel AL, Peyrot des Gachons C, Plank KL, Alarcon S, Breslin PA. Individual differences in AMY1 gene copy number, salivary α-amylase levels, and the perception of oral starch. *PLoS One* 5:e13352, 2010.

7. Pedersen AM, Bardow A, Jensen SB, Nauntofte B. Saliva and gastrointestinal functions of taste, mastication, swallowing and digestion. *Oral Dis* 8: 117-129, 2002.

8. Read NW, Welch IM, Austen CJ et al. Swallowing food without chewing; a simple way to reduce postprandial glycemia. *Br J Nutr* 55: 43-47, 1986.

9. Suzuki H, Fukushima M, Okamoto S et al. Effects of thorough mastication on postprandial plasma glucose concentrations in nonobese Japanese subjects. *Metabolism* 54: 1593-1599, 2005.

10. Zhu Y, Hsu WH, Hollis JH. Increasing the number of masticatory cycles is associated with reduced appetite and altered postprandial plasma concentrations of gut hormones, insulin and glucose. *Br J Nutr* 110: 384-390, 2013.

11. Mandel AL, Breslin PA. High endogenous salivary amylase activity is associated with improved glycemic homeostasis following starch ingestion in adults. *J Nutr* 142: 853-858, 2012.

12. Sakamoto Y, Kato S, Sekino Y et al. Change of gastric emptying with chewing gum: evaluation using a continuous real-time C breath test (BreathID system). *J Neurogastroenterol Motil* 17: 174-179, 2011.

13. Li J, Zhang N, Hu L et al. Improvement in chewing activity reduces energy intake in one meal and modulates plasma gut hormone concentrations in obese and lean young Chinese men. *Am J Clin Nutr* 94: 709-716, 2011.

14. Ohmure H, Takada H, Nagayama K, Sakiyama T, Tsubouchi H, Miyawaki S. Mastication suppresses initial gastric emptying by modulating gastric activity. *J Dent Res* 91: 293-298, 2012.

15. Morey S, Shafat A, Clegg ME. Oral versus intubated feeding and the effect on glycemic and insulinemic responses, gastric emptying and satiety. *Appetite* 96: 598-603, 2016.

16. Cohen J. *Statistical power analysis for the behavioural sciences. 2nd ed*. Lawrence Erlbaum Associates, Hillsdale, 1988.

17. Rosenblum JL, Irwin CL, Alpers DH. Starch and glucose oligosaccharides protect salivary-type amylase activity at acid pH. *Am J Physiol* 254(5 Pt 1): 775-780, 1988.

18. Björck I, Granfeldt Y, Liljeberg H, Tovar J, Asp NG. Food properties affecting the digestion and absorption of carbohydrates. *Am J Clin Nutr* 59 Suppl 3: S699–705, 1994.

19. Hoebler C, Karinthi A, Devaux MF et al. Physical and chemical transformations of cereal food during oral digestion in human subjects. *Br J Nutr* 80: 429-436, 1998.

20. Granfeldt Y, Nyberg L, Björck I. Muesli with 4 g oat beta-glucans lowers glucose and insulin responses after a bread meal in healthy subjects. *Eur J Clin Nutr* 62: 600-607, 2008.

21. Helman CA. Chewing gum is as effective as food in stimulating cephalic phase gastric secretion. *Am J Gastroenterol* 83: 640-642, 1988.

22. Woolnough JW, Bird AR, Monro JA, Brennan CS. The effect of a brief salivary α-amylase exposure during chewing on subsequent in vitro starch digestion curve profiles. *Int J Mol Sci* 11: 2780-2790, 2010.

23. Ranawana V, Clegg ME, Shafat A, Henry CJ. Postmastication digestion factors influence glycemic variability in humans. *Nutr Res* 31: 452-459, 2011.

24. Kresge DL, Melanson K. Chewing gum increases energy expenditure before and after controlled breakfasts. *Appl Physiol Nutr Metab* 40: 401-406, 2015.

25. Teff KL, Levin BE, Engelman K. Oral sensory stimulation in men: effects on insulin, C-peptide, and catecholamines. *Am J Physiol* 265(6 Pt 2): 1223-1230, 1993.

26. Teff KL, Engelman K. Oral sensory stimulation improves glucose tolerance in humans: effects on insulin,

C-peptide, and glucagon. *Am J Physiol* 270(6 Pt 2): 1371-1379, 1996.

27. Zhu Y, Hsu WH, Hollis JH. Modified sham feeding of foods with different macronutrient compositions differentially influences cephalic change of insulin, ghrelin, and NMR-based metabolomic profiles. *Physiol Behav* 135: 135-142, 2014.

28. Lorentzen M, Madsbad S, Kehlet H, Tronier B. Effect of sham-feeding on glucose tolerance and insulin secretion. *Acta Endocrinol (Copenh)* 115: 84-86, 1987.

29. Andersen HB, Christiansen E, Vølund A et al. Sham feeding increases glucose tolerance by a mechanism independent of insulin secretion in normal subjects. *Digestion* 56: 253-258, 1995.

30. Teff KL. Cephalic phase pancreatic polypeptide responses to liquid and solid stimuli in humans. *Physiol Behav* 99: 317-323, 2010.

31. Katschinski M. Nutritional implications of cephalic phase gastrointestinal responses. *Appetite* 34: 189-196, 2000.

32. Suez J, Korem T, Zeevi D et al. Artificial sweeteners induce glucose intolerance by altering the gut microbiota. *Nature* 514: 181-186, 2014.