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Original article

Impact of different timing of consuming sweet snack on postprandial glucose excursions in healthy women

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ABSTRACT

Aims. – Our aim was to evaluate the acute effect of eating sweet snacks at different times of day on glycaemic parameters in young women without diabetes.
Methods. – In this randomized controlled three-treatment crossover study, 17 women [(means ± SD) age: 21.2 ± 0.8 years, BMI: 20.7 ± 2.5 kg/m2, HbA_{1c}: 36 ± 2 mmol/mol (5.1 ± 0.2%)] wore flash (continuous) glucose monitoring systems for 7 days. Each participant consumed identical test meals on days 4, 5 and 6, but consumed sweet snacks (baked cake: 498 kcal; 53.6 g of carbohydrate, 8.0 g of protein, 28.0 g of fat) at 12:30 (post-lunch), 15:30 (mid-afternoon) and 19:30 (post-dinner), respectively, on each of those days. Daily glycaemic parameters on those 3 days of snacking at different times of day were compared within-participant.
Results. – The mean amplitude of glycaemic excursions (3.54 ± 0.32 vs. 2.73 ± 0.20 mmol/L; $P < 0.05$), standard deviation of glucose (1.20 ± 0.11 vs. 0.92 ± 0.07 mmol/L; $P < 0.05$), incremental area under the curve (IAUC) for glucose at 12:00–07:00 (986 ± 89 vs. 716 ± 88 mmol/L × min; $P < 0.05$) and IAUC at 07:00–10:00 the next day (141 ± 17 vs. 104 ± 12 mmol/L × min; $P < 0.05$) when the snack was eaten post-dinner were all significantly higher than with mid-afternoon snacking.
Conclusion. – Eating sweet snacks post-dinner should be avoided because it worsens glucose excursions as well as postprandial glucose levels after both dinner and the following day's breakfast in young healthy (non-diabetic) women.

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Introduction

Lifestyle modifications, especially dietary ones, can decrease the risk of developing type 2 diabetes (T2D) [1]. Postprandial hyperglycaemia is associated with increased risk of T2D and cardiovascular disease even before the onset of diabetes [2–4]. Acute blood glucose fluctuations suppress endothelium-dependent vasodilation [5] and increase levels of tumour necrosis factor (TNF)-α, interleukin (IL)-6 [6] and platelet aggregation [7] in healthy people. Therefore, decreasing postprandial hyperglycaemia reduces the risk of developing cardiovascular disease and T2D.

It has been demonstrated that the consumption of snacks leads to weight gain [8] and greater risk of T2D [9,10] because snacking encourages higher energy (caloric) intakes by increasing food stimuli, hunger and the desire to eat [11]. Also, commercial sweet snacks are usually poor in nutritional value because they are high in energy, and contain refined carbohydrates, large amounts of sugar and fat, and low amounts of dietary fibre, vitamins and minerals.

The World Health Organization (WHO) recommends decreasing sugar and fat intakes for health benefits in all population groups [12,13], while the consumption of sweet snacks of low nutritional value is not recommended for anyone. However, Heller et al. [14] reported that 77% of people with either type 1 diabetes (T1D) or T2D consumed snacks and that most patients enjoyed snacking. Indeed, the Japanese government reported that around 60% of female Japanese university

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students consumed snacks every day, while 40% of male Japanese university students did so. In addition, > 80% of female university students consumed snacks two to six times a week [15].

Epidemiological and clinical studies have indicated that nut consumption can be a healthy dietary approach for preventing T2D because eating nuts improves glycaemic control and reduces postprandial glycaemic responses [16,17]. However, snacking on nuts is not favoured by everyone. In fact, it can be difficult for some people to replace sweet snacks with nuts or other low glycaemic index (GI) foods, or to stop eating sweet snacks entirely. Indeed, snacking is strongly related to psychological satisfaction and quality of life [18], even though many people are aware that consumption of sweet snacks leads to body weight gain and raises the risk of metabolic disorders.

Our group recently reported that consuming snacks at different times of day changed glycaemic responses: eating a 75-kcal snack at mid-afternoon (15:30) decreased the mean amplitude of glycaemic excursions (MAGE) compared with eating the snack post-lunch (12:30) in people with T2D [19]. Moreover, it was also shown that having a late-night dinner (21:00) increased postprandial hyperglycaemia and glucose excursions, whereas splitting dinner into two stages – eating carbohydrates early in the evening (18:00) followed by vegetables and the main dish (protein) later on (21:00) – significantly ameliorated daily glucose excursions and postprandial hyperglycaemia in both people with and without diabetes [20,21].

However, the effect of eating sweet snacks at different times of day on glycaemic responses has not been extensively studied in people without diabetes. Thus, the aim of the present study was to evaluate the acute effect of eating sweet snacks at different times of day on glycaemic parameters, as obtained by flash (continuous) glucose monitoring (FGM), in young healthy (non-diabetic) women. The FGM system used for glycaemic measurement in this study has been reported to be an accurate and effective replacement for self-monitoring of blood glucose [22–24].

Methods

Participants

A total of 19 female students at Kyoto Women's University in Kyoto, Japan, volunteered and were informed of the study requirements, which was conducted between July 2017 and January 2018. These volunteers had to have no history of any metabolic disease. In addition, none of these women could be pregnant or smokers, or have any eating disorders, weight loss or other special diet within the past 6 months; all also had to refrain from taking any medications or supplements known to affect metabolism. The purpose, design and risks of the study were explained to each participant, and written informed consent was obtained from each volunteer prior to starting the study.

Study design

The study protocol was approved by the Ethics Committee of Kyoto Women's University according to guidelines laid down by the Declaration of Helsinki, and was registered on Clinical Trial gov. (UMIN 000009465). This was a randomized controlled three-treatment crossover within-participant clinical trial. The study protocol was explained to each participant prior to the study, and all participants received phone calls during the study period by clinic dietitians to ensure adherence to the study protocol (Fig. 1).

All participants had to wear an FGM device (FreeStyle Libre Pro, Abbott Laboratories, Abbott Park, IL, USA) on the back of their left upper arm under physician management at Kyoto Women's University. During the 7-day test period, each participant consumed identical test meals (total energy: 2054 kcal; protein: 70.8 g; fat: 70.2 g; carbohydrate: 287.3 g) for breakfast at 07:00, lunch at 12:00 and dinner at 19:00 at home from study days 2 to 6 (Table 1). Half the participants consumed their snacks at 12:30 (post-lunch) on day 4, at 15:30 (mid-afternoon) on day 5 and at 19:30 (post-dinner) on day 6 at home. The other half of participants consumed their snacks post-dinner on day 4, in the

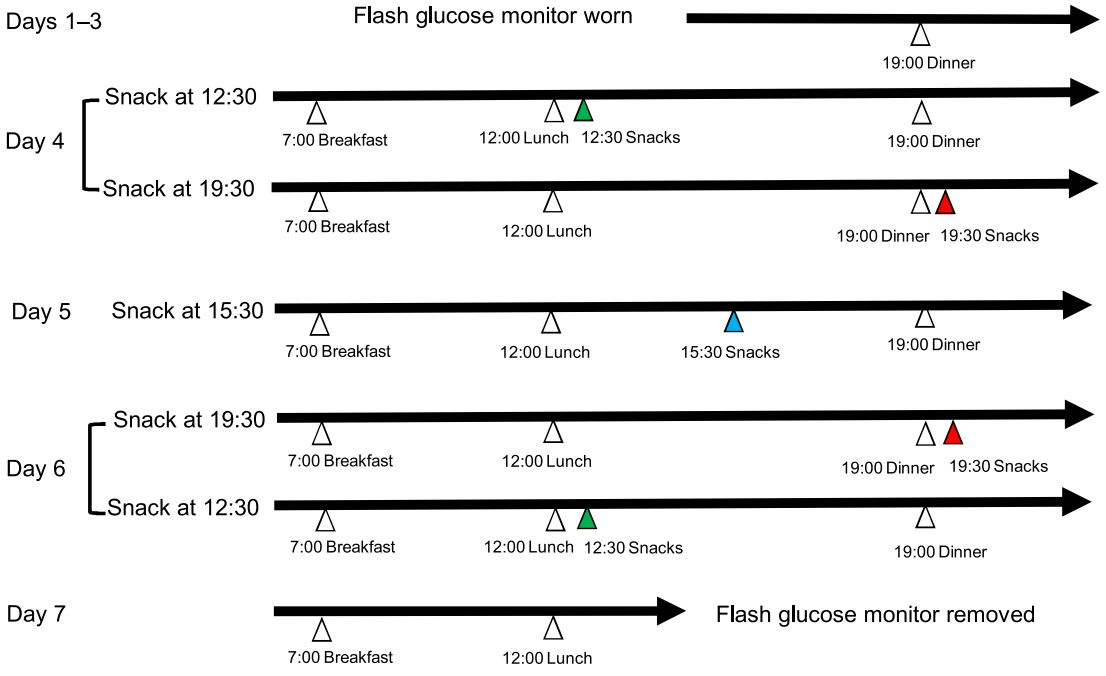

Fig. 1. The 7-day study protocol: all participants consumed identical test meals, while wearing flash (continuous) glucose monitoring devices, for 3 days of breakfast at 07:00, lunch at 12:00 and dinner at 19:00, while snacking at 12:30 (post-lunch) on day 4, at 15:30 (mid-afternoon) on day 5 and at 19:30 (post-dinner) on day 6, or at 19:30 on day 4 and at 12:30 on day 6.

Table 1
Composition and macronutrient contents of study test meals.

	Energy (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	Fibre (g)	Contents in detail
Breakfast	351	15.5	10.6	54.2	5.0	White bread 60 g, tomato 100 g, broccoli 60 g, milk 200 g, strawberry jam (sugar-free) 13 g
Lunch	549	23.2	11.2	87.5	7.8	Boiled white rice 150–200 g, frozen meal box of fried fish with vegetable, tomato 100 g, spinach 80 g
Dinner	656	24.1	20.4	92.0	8.2	Boiled white rice 150–200 g, seasoned seaweed, tomato 100 g, frozen meal box of gluten steak with vegetable, spinach 80 g with fried tofu 15 g
Snack	498	8.0	28.0	53.6	0	Baked cake 120 g
Total	2054	70.8	70.2	287.3	21.0	

mid-afternoon on day 5 and post-lunch on day 6. All participants were assigned to their group by flipping a coin. On day 7, all had their FGM devices removed under physician instruction at Kyoto Women's University.

The composition and nutritional content of the test meals were analyzed by computer software (Excel Eiyo-Kun, Kenpakusya, Tokyo, Japan). The energy ratios of these meals was 56%, 14% and 30% from carbohydrate, protein and fat, respectively. Meals consisted of boiled white rice, white bread, milk, tomato (100 g × 3), spinach (80 g × 2), broccoli (60 g), a frozen food box of gluten 'steak' and fried fish with vegetable (Tokatsu Foods Co., Ltd, Yokohama, Japan), and a 498-kcal baked cake snack (carbohydrate: 53.6 g; protein: 8.0 g; fat: 28.0 g).

All test meals had the same macronutrient content and composition. The frozen food boxes (for lunch and dinner) and the snack were provided by the research group, whereas the rest of the test food was prepared by the participants according to a brochure prepared for each participant by our clinic dietitians. The frozen food boxes were kept in a freezer and heated in a microwave at 600 W for 2–3 min by each participant at home. The boiled white rice was measured to an exact amount between 150 and 200 g, which was designed to meet the caloric requirement of each participant (calculated as 30 kcal/kg body weight/day).

All test meals, including the cooked rice, were heated by microwave by each participant before consumption. Each participant weighed all their food and consumed all test meals and snacks at the times specified by the study protocol. None were allowed to eat or drink anything other than the test meals except for water, green tea, or black tea and coffee with no sugar or milk during the study period. All participants were also asked to avoid alcohol and excessive physical activity for 2 days prior to and during the study period.

The participants' food consumption was controlled as follows: the first dish of vegetables was consumed for 5 min, the main dish for 5 min and rice/bread for 5 min at each meal; and all test meals had to be consumed within 20 min [20]. All participants were also instructed to follow the study protocol strictly during the study period, and all records of food amounts and meal times were assessed for the required compliance with the study protocol by the dietitians, who excluded any participants who failed to follow the protocol. Thus, all analyzed participants consumed identical test meals and snacks for 3 days except for snacking at different times of day. FGM data were recorded and all daily glucose parameters measured during the study period were compared.

Measurements

Two weeks prior to starting the study, participants' anthropometric measurements and blood samples were collected in the morning after an overnight fast. Fasting whole blood glucose was measured using amperometric methods. Haemoglobin A_{1c} (HbA_{1c}) levels were determined by high-performance liquid chromatography (HPLC). Incremental areas under the curve (IAUCs) for glucose after lunch and dinner at 12:00 and 19:00, respectively, were calculated from baseline values, using the trapezoidal rule. Parameters to evaluate glycaemic variability included MAGE, large amplitude of glycaemic excursions (LAGE), standard deviation (SD) of glucose, percentage coefficient of variation (CV) for glucose (obtained by computing the following: SD of glucose/mean glucose × 100 [25]), and maximum (MAX) and minimum (MIN) glucose levels. MAGE, LAGE and glucose SD were also calculated from 12:00 to 12:00 the next day as described previously [26]. These glucose parameters were compared within each participant for the 3 days of consuming identical meals except for snacking at different times of day.

Sample size and statistical analyses

A sample size of 14 participants conferred an 80% power to detect a 5% difference in MAGE, based on our previous study of snacking at different times in patients with T2D [19]. For the present study, 19 participants were enrolled, but two were excluded because of non-adherence to the study protocol. Thus, our present results are based on 17 women.

Primary outcomes were mean blood glucose, SD of glucose, MAGE and LAGE, while secondary outcomes were postprandial glucose and IAUC for glucose. Also, as a normal distribution and homogeneity of all glycaemic parameters could not be confirmed by Shapiro-Wilk and Levene tests, paired comparisons were performed instead, using the Wilcoxon matched-pairs signed-rank test, followed by post-hoc Bonferroni inequality ($P < 0.017$) when Friedman's test revealed significant effects for glucose parameters ($P < 0.05$). Results are reported as means ± SEM (standard error of the mean) unless otherwise stated. All analyses were performed with SPSS Statistics version 22 software (IBM Corp., Armonk, NY, USA).

Results

Two participants were excluded: one could not eat test meals on time; and the other could not finish the entire test meal. Thus,

Table 2
Characteristics of study participants without diabetes (n = 17).

Women	17
Age (years)	21.2 ± 0.8
Height (cm)	159.6 ± 6.3
Body weight (kg)	52.9 ± 8.4
Body mass index (kg/m^2)	20.7 ± 2.5
HbA_{1c} [(mmol/mol)%]	36 ± 2 (5.1 ± 0.2)
Fasting plasma glucose (mmol/L)	4.9 ± 0.7
Systolic blood pressure (mmHg)	106 ± 8
Diastolic blood pressure (mmHg)	64 ± 7
Family history of diabetes	
Father	0
Mother	0
Grandfather	3
Grandmother	4

Data are means ± SD or n.

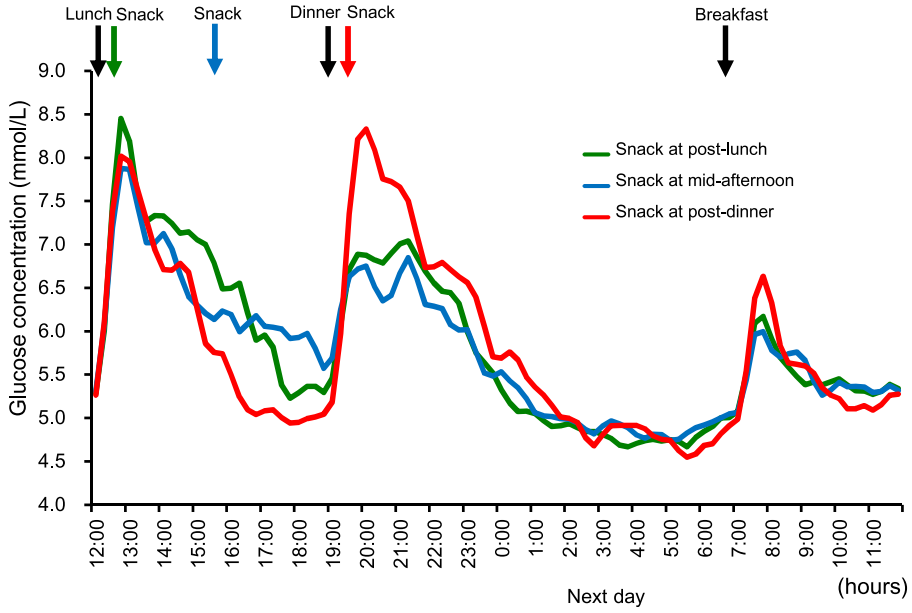

Fig. 2. The mean glucose profile during the study period in healthy young women (n = 17) on the day they consumed snacks at 12:30 (post-lunch), 15:30 (mid-afternoon) and 19:30 (post-dinner).

17 women completed the study, and their characteristics are shown in Table 2. Their MAGEs, SDs of glucose, CVs, IAUC at 12:00-07:00, and IAUC at 07:00-10:00 the next day when snacking post-dinner (19:30) were all significantly higher compared with their values when snacking in the mid-afternoon (15:30), even though mean glucose levels did not differ with different timings of snacking (Fig. 2, Table 3). In addition, the IAUC at 12:00–07:00 when snacking in the mid-afternoon (15:30) tended to be lower than when snacking post-lunch (12:30).

Discussion

Our present study has demonstrated that the consumption of identical test meals and an identical sweet snack (498 kcal) post-dinner resulted in greater daily glucose excursions compared with snacking in the mid-afternoon. Even though all test meals were identical in nutrient composition, differences in the timing of eating the sweet snacks produced significant differences overall in glucose excursions in healthy young Japanese women, a remarkable finding. Moreover, the glycaemic response to consuming a sweet snack post-dinner also affected the IAUC after breakfast the next day. As wide glucose fluctuations are known to be risk factors for cardiovascular disease and T2D in both those with and without diabetes [2–4,25], this study has clearly demonstrated that eating sweet snacks after dinner should be avoided in healthy young women. On the other hand, eating a sweet snack in the mid-afternoon (between lunch and dinner) ameliorates post-meal glycaemic responses compared with eating such snacks after dinner, although the consumption of sweet snacks is not recommended for anyone. To our knowledge, this is the first study to report that eating sweet snacks at different times of day leads to a significant difference in glucose excursions in healthy people, just as it does in people with T2D [19].

One possible reason for the greater glycaemic excursions when eating sweet snacks post-dinner may be related to the body's natural circadian rhythm. The higher postprandial glucose levels observed with sweet-snacking post-dinner might be related to

Table 3
Glucose parameters in young healthy women (n = 17).

	Snack at 12:30 (post-lunch)	Snack at 15:30 (mid-afternoon)	Snack at 19:30 (post-dinner)	P (19:30 vs. 15:30)	P (19:30 vs. 12:30)	P (12:30 vs. 15:30)
Mean glucose level (mmol/L)	5.81 (0.09)	5.77 (0.11)	5.80 (0.12)	0.629	0.629	0.629
SD of glucose (mmol/L)	1.08 (0.11)	0.92 (0.07)	1.20 (0.11)	0.002	0.210	0.077
CV for glucose (%)	18.6 (1.8)	16.1 (1.4)	20.3 (2.0)	0.002	0.629	0.332
MAGE (mmol/L)	3.03 (0.27)	2.73 (0.20)	3.54 (0.32)	0.013	0.049	0.332
MAX glucose (mmol/L)	8.98 (0.38)	8.51 (0.32)	9.13 (0.39)	0.049	0.210	0.454
MIN glucose (mmol/L)	4.34 (0.14)	4.41 (0.13)	4.23 (0.18)	0.118	0.804	0.629
LAGE (mmol/L)	4.64 (0.40)	4.11 (0.33)	4.91 (0.45)	0.077	0.332	0.332
IAUC 12:00–07:00 (mmol/L × min)	870 (112)	716 (88)	986 (89)	0.013	0.332	0.049
IAUC 07:00–10:00 (mmol/L × min)	105 (8.6)	104 (12)	141 (17)	0.013	0.210	1.000

Data are means (SEM) as calculated by Wilcoxon's matched-pairs signed-rank test; MAGE, LAGE, SD, CD, MAX, MIN calculated as described in main text; IAUC calculated using trapezoidal rule as area under the curve for glucose above baseline value at 12:00 (lunch) and 19:00 (dinner).
SD: standard deviation; CV: coefficient of variation; MAGE: mean amplitude of glycaemic excursions; MAX: maximum; MIN: minimum; LAGE: large amplitude of glycaemic excursions; IAUC: incremental area under the curve.

diurnal variations in insulin resistance and plasma free fatty acid (FFA) concentrations. Some research has indicated that insulin resistance is higher at night than in the morning or during the day [27]. In addition, with longer fasting, which was 6.5 h between lunch and dinner in our present study, plasma FFA concentrations are increased, and higher FFA concentrations had negative effects on insulin sensitivity when participants consumed snacks post-dinner. Moreover, there are also reports that glucagon-like peptide (GLP)-1 secretion is influenced by diurnal rhythms independently of food intake [28,29].

However, our present study has only demonstrated the acute effects of different timings of consuming sweet snacks on glycaemic parameters and, thus, further investigations are now required to determine the underlying mechanisms, including the secretion of insulin, glucagon and incretin hormones.

One reason for the improvement in glucose excursions when snacking in the mid-afternoon rather than post-dinner or post-lunch may be explained by the smaller amount of carbohydrates in each meal: postprandial glucose levels are usually influenced by meal size, particularly the amount of carbohydrates [30,31]. Thus, in our study, the amounts of carbohydrate when snacking post-lunch and post-dinner were 141.1 g and 145.6 g, respectively (lunch: 87.5 g, dinner 92.0 g, snack 53.6 g), whereas consumption of the snack alone at mid-afternoon amounts to only 53.6 g of carbohydrate. Thus, the IAUC at 12:00–07:00 was significantly lower when snacking in the mid-afternoon compared with post-dinner, and tended to be lower than when snacking post-lunch.

In addition, another reason why the IAUC at 12:00-07:00 was lower when snacking in the mid-afternoon compared with post-lunch or post-dinner might be the 'second meal effect'. In this case, the first and second phases of insulin release may have been enhanced by the previous glucose response to eating a snack at 15:30 (mid-afternoon), 3 h from lunch and from dinner, whereas postprandial glucose levels after dinner were restrained by the second meal [32,33]. However, such a second meal effect is still hypothetical, as its confirmation would require plasma insulin measurements at both pre- and post-meal as well as the glycaemic responses.

Nevertheless, our present study has demonstrated that eating a sweet snack post-dinner increases glucose excursions and postprandial glucose levels both post-dinner and after the following morning's breakfast compared with eating a sweet snack in the mid-afternoon. Thus, eating sugar- and fat-rich snacks should be avoided by everyone, including healthy young women. Moreover, even if some people may find it difficult to replace a sweet snack with nuts or low GI foods, eating a sweet snack 3–4 h away from lunch might be a practical means of suppressing large daily glucose excursions, as shown in the present study.

This hypothesis appears to be consistent with our previous studies in which dinner was divided, resulting in four instead of three meals per day, to reduce glycaemic excursions in both those with and without T2D [20,21]. In addition, some studies have demonstrated that eating more frequently improves glucose control in people with and without diabetes [34–36]. Therefore, it may be more beneficial to decrease glycaemic excursions by dividing meals into smaller portions while maintaining an identical total nutrient intake per day.

One limitation of the present study, as with all dietary acute interventional studies, is the inability to translate these effects into long-term clinical benefits. It should also be mentioned that, besides the timing of consumption, the macronutrient composition of snacks might also affect glycaemic control [36]. In addition, while glucose excursions with different timings of consuming small snacks (75-kcal biscuits) failed to produce any difference in healthy individuals (data not shown), a significant difference was observed when such snacks were consumed post-lunch and mid-afternoon in people with T2D [19]. Another limitation is that the study population comprised only healthy Japanese women, making it unclear whether the present results can be appropriately applied to people with diabetes, to healthy men and to other racial groups. Finally, the mechanisms underlying metabolic regulation, including insulin and incretin hormone secretion and endogenous glucose production, also remain unclear.

Nevertheless, the disadvantages of eating sweet snacks post-dinner, as shown in this study, raise the possibility of a greater risk of cardiovascular disease and T2D in otherwise healthy young women. However, additional investigations are as yet still required to elucidate the mechanisms behind our study findings and the long-term effects on metabolic control in people without T2D.

Conclusion

This study has demonstrated that eating sweet snacks post-dinner worsens glucose excursions as well as postprandial glucose levels after both dinner and the following morning's breakfast. Thus, consuming sweet snacks after dinner should always be avoided in healthy young women.

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Authors' contributions

A.N. contributed to data collection, performed the data analysis and contributed to the writing of the article. S.I. designed the study, recruited participants, conducted the experiments, performed the data analysis and wrote the article. S.K. conducted the experiments, contributed to the discussion and reviewed the article. T.M. performed the data analysis and contributed to writing the article. S.M., N.O., Y.H., M.T., S.K. and M.F. contributed to the discussion and reviewed the article. S.K. and S.I are guarantors of this work and, as such, had full access to all study data and take responsibility for the integrity of the data and accuracy of the data analysis. All authors approved the final version of the article.

Prior presentation

This study was presented at the 54th Annual Meeting of the European Association for the Study of Diabetes (EASD) in Berlin, 1-5 October 2018.

Disclosure of interest

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References

[1] Thomas T, Pfeiffer AF. Foods for the prevention of diabetes: how do they work? Diabetes Metab Res Rev 2012;28:25–49.
[2] Torimoto K, Okada Y, Mori H, Tanaka Y. Relationship between fluctuations in glucose levels measured by continuous glucose monitoring and vascular endothelial dysfunction in type 2 diabetes mellitus. Cardiovasc Diabetol 2013;12:1–7.
[3] Cederberg H, Saukkonen T, Laakso M, Jokelainen J, Härkönen P, Timonen M, et al. Postchallenge glucose, A1C, and fasting glucose as predictors of type 2 diabetes and cardiovascular disease: a 10-year prospective cohort study. Diabetes Care 2010;33:2077–83.
[4] Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata diabetes study. Diabetes Care 1999;22:920–4.
[5] Kawano H, Motoyama T, Hirashima O, Hirai N, Miyao Y, Sakamoto T, et al. Hyperglycemia rapidly suppresses flow-mediated endothelium-dependent vasodilation of brachial artery. J Am Coll Cardiol 1999;34:146–54.
[6] Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, et al. Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: role of oxidative stress. Circulation 2002;106:2067–72.
[7] Sakamoto T, Ogawa H, Kawano H, Hirai N, Miyamoto S, Takazoe K, et al. Rapid change of platelet aggregability in acute hyperglycemia. Detection by a novel laser-light scattering method. Thromb Haemost 2000;83:475–9.
[8] van der Heijden AA, Hu FB, Rimm EB, van Dam RM. A prospective study of breakfast consumption and weight gain among U.S. men. Obesity (Silver Spring) 2007;15:2463–9.
[9] Mekary RA, Giovannucci E, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in men: breakfast omission, eating frequency, and snacking. Am J Clin Nutr 2012;95:1182–9.
[10] Mekary RA, Giovannucci E, Cahill L, Willett WC, van Dam RM, Hu FB. Eating patterns and type 2 diabetes risk in older women: breakfast consumption and eating frequency. Am J Clin Nutr 2013;98:436–43.
[11] Effects of increased meal frequency on fat oxidation and perceived hunger. Obesity (Silver Spring) 2013;21:336–343.
[12] World Health Organization. In: Diet, nutrition and the prevention of chronic diseases: report of a Joint WHO/FAO Expert Consultation. WHO Technical Report Series, No. 916. Geneva: World Health Organization; 2003.
[13] World Health Organization. In: Guideline: Sugars intake for adults and children. Geneva: World Health Organization; 2015.
[14] Heller T, Kloos C, Keßler D, Müller N, Thierbach R, Wolf G, et al. Use of snacks in insulin-treated people with diabetes mellitus and association with HbA_{1c}, weight and quality of life: a cross sectional study. Diabet Med 2015;32:353–8.
[15] Cabinet Office, Government of Japan, http:// warp.da.ndl.go.jp/ info:ndljp/ pid/ 998219/www8.cao.go.jp/syokuiku/more/research/pdf/syoku-report.pdf/; 2009.
[16] Hernández-Alonso P, Camacho-Barcia L, Bulló M, Salas-Salvadó J. Nuts and dried fruits: an update of their beneficial effects on type 2 diabetes. Nutrients 2017;28:9 [pii: E673].
[17] Kim Y, Keogh JB, Clifton PM. Benefits of nut consumption on insulin resistance and cardiovascular risk factors: multiple potential mechanisms of actions. Nutrients 2017;22:9 [pii:E1271].
[18] Kahleova H, Belinova L, Hill M, Pelikanova T. Do patients with type 2 diabetes still need to eat snacks? Eur J Cline Notre 2015;69:755–6.
[19] Imai S, Kajiyama S, Hashimoto Y, Nitta A, Miyawaki T, Matsumoto S, et al. Consuming snacks at mid-afternoon compared with just after lunch improves mean amplitude of glycaemic excursions in patients with type 2 diabetes: a randomized cross-over clinical trial. Diabetes Metab, [pii: S1262-3636(18)30122-8, doi: 10.1016].
[20] Imai S, Kajiyama S, Hashimoto Y, Yamane C, Miyawaki T, Ozasa N, et al. Divided consumption of late-night-dinner improves glycemic excursions in patients with type 2 diabetes: a randomized cross-over clinical trial. Diabetes Res Clinical Pract 2018;136:78–84.
[21] Kajiyama S, Imai S, Hashimoto Y, Yamane C, Miyawaki T, Matsumoto S, et al. Divided consumption of late-night-dinner improves glycemic excursions in young healthy women: a randomized cross-over clinical trial. Diabetes Res Clinical Pract 2018;136:78–84.
[22] Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multi-centre, non-masked, randomised controlled trial. Lancet 2016;388:2254–63.
[23] Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Use of flash glucose-sensing technology for 12 months as a replacement for blood glucose monitoring in insulin-treated type 2 diabetes. Diabetes Ther 2017;8:573–86.
[24] Oskarsson P, Antuna R, Geelhoed-Duijvestijn P, Kŕger J, Weitgasser R, Bolinder J. Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. Diabetologia 2018;61:539–50.
[25] Dasari PS, Gandomani BS, Teague AM, Pitale A, Otto M, Short KR. Glycaemic variability is associated with markers of vascular stress in adolescents. J Pediatr 2016;172:47–55.
[26] Rodbard D. New and improved methods to characterize glycaemic variability using continuous glucose monitoring. Diabetes Technol Ther 2009;11:551–65.
[27] Morgan LM, Aspostolakou F, Wright J, Gama R. Diurnal variations in peripheral insulin resistance and plasma nonesterified fatty acid concentrations: a possible link? Ann Clin Biochem 1999;36(4):447–50.
[28] Gil-Lozano M, Mingomataj EL, Wu WK, Ridout SA, Brubaker PL. Circadian secretion of the intestinal hormone GLP-1 by the rodent L cell. Diabetes 2014;63:3674–85.
[29] Williams DL, Baskin DG, Schwartz MW. Evidence that intestinal glucagon-like peptide-1 plays a physiological role in satiety. Endocrinology 2009;150:1680–7.
[30] Bell KJ, Barclay AW, Petocz P, Colagiuri S, Brand-Miller JC. Efficacy of carbohydrate counting in type 1 diabetes: a systematic review and meta-analysis. Lancet Diabetes Endocrinol 2014;2:133–40.
[31] Sheard NF, Clark NG, Brand-Miller JC, Franz MJ, Pi-Sunyer FX, Mayer-Davis E, et al. Dietary carbohydrates (amount and type) in the prevention and management of diabetes: a statement by the American Diabetes Association. Diabetes Care 2004;27:2266–71.
[32] Bonuccelli S, Muscelli E, Gastaldelli A, Barsotti E, Astiarraga BD, Holst JJ, et al. Improved tolerance to sequential glucose loading (Staub-Traugott effect): size and mechanisms. Am J Physiol Endocrinol Metab 2009;297:E532–7.
[33] Clark CA, Gardiner J, McBurney MI, Anderson S, Weatherspoon LJ, Henry DN, et al. Effects of breakfast meal composition on second meal metabolic response in adults with type 2 diabetes mellitus. Eur J Clin Nutr 2006;60:1122–9.
[34] Jenkins DJ, Ocana A, Jenkins AL, Wolever TM, Vuksan V, Katzman L, et al. Metabolic advantages of spreading the nutrient load: effects of increased meal frequency in non-insulin-dependent diabetes. Am J Clin Nutr 1992;55:461–7.
[35] Leidy HJ, Campbell WW. The effect of eating frequency on appetite control and food intake: brief synopsis of controlled feeding studies. J Nutr 2011;141:154–7.
[36] Kanaley JA, Heden TD, Liu Y, Fairchild TJ. Alteration of postprandial glucose and insulin concentrations with meal frequency and composition. Br J Nutr 2014;112:1484–93.