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Divided consumption of late-night-dinner improves glycemic excursions in patients with type 2 diabetes: A randomized cross-over clinical trial

Saeko Imai [a,*], Shizuo Kajiyama [b,c], Yoshitaka Hashimoto [c], Chikako Yamane [d], Takashi Miyawaki [a], Neiko Ozasa [e], Muhei Tanaka [c], Michiaki Fukui [c]

[a] Department of Food and Nutrition, Kyoto Women's University, Kyoto, Japan
[b] Kajiyama Clinic, Kyoto, Japan
[c] Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, Japan
[d] St. Mary's Hospital, Himeji, Japan
[e] Department of Cardiovascular Medicine, Kyoto University, Graduate School of Medicine, Kyoto, Japan

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ABSTRACT

Aims: To explore the acute effect of late-night-dinner and divided dinner on postprandial glucose levels in patients with type 2 diabetes.

Methods: Sixteen patients were randomly assigned to this cross-over study. Each patient wore a continuous glucose monitor for 5 days and consumed identical test meals for 3 days. Patients consumed the test meals of dinner at 2100 h (D21) or divided dinner (vegetable and rice at 1800 h and the vegetable and the main dish at 2100 h) on the second or fourth day, and dinner at 1800 h (D18) on the third day. The daily glucose parameters were compared within-patient for 3 days.

Results: D21 demonstrated significantly higher values of incremental area under the curve (IAUC) for glucose 2300 to 0800 h (644 ± 156 vs. 147 ± 63 mmol/L × min, $p < 0.01$, mean ± standard error of the mean) and incremental glucose peak (IGP) after dinner (6.78 ± 0.79 vs. 3.09 ± 0.62 mmol/L, $p < 0.01$) compared to those of D18. Moreover, the mean amplitude of glycemic excursion (MAGE) of D21 tended to be higher than that of D18 (6.99 ± 0.60 vs. 5.35 ± 0.51 mmol/L, $p = 0.077$). However, the divided dinner significantly reduced IAUC 2300 to 0800 h (142 ± 60 mmol/L × min, $p < 0.01$), IGP after dinner (3.75 ± 0.58 mmol/L, $p < 0.01$), and MAGE (5.33 ± 0.41 mmol/L, $p < 0.01$) compared to those of D21.

Conclusion: Our findings demonstrated that consuming late-night-dinner led to postprandial hyperglycemia, and this postprandial hyperglycemia can be ameliorated by consuming a divided dinner.

* Corresponding author. Department of Food and Nutrition, Kyoto Women's University, 35, Kitahiyoshi-cho, Imakumano, Higashiyama-ku, 605-8501 Kyoto, Japan.
E-mail address: imais@kyoto-wu.ac.jp (S. Imai).

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1. Introduction

Postprandial hyperglycemia plays a major role in micro and macrovascular complications in patients with type 2 diabetes [1–5], and reducing postprandial hyperglycemia is thus an important goal for patients with type 2 diabetes. Postprandial glucose levels are influenced by meal size, the amount of carbohydrates [6,7], the macronutrient composition [8], intestinal absorption [9], hormone secretion, gastric emptying [10, 11], and food order [12, 13]. Unhealthy habits such as skipping breakfast and late-night eating have been shown to be associated with weight gain and obesity [14–17]. However, the effect of the late-night-dinner on postprandial glucose levels has not been extensively studied in patients with type 2 diabetes.

We hypothesized that late-night-dinners would increase postprandial glucose levels in patients with type 2 diabetes. Therefore, in this randomized controlled, a within-patient, cross-over study, we assessed the effect of late-night-dinner on the postprandial glucose levels in patients with type 2 diabetes.

2. Methods

2.1. Patients

Interested patients were initially screened and informed of study requirements from the outpatient at Kajiyama Clinic, Kyoto, Japan. The period of recruitment and the study period was from September 2014 to April 2015. We included the patients with type 2 diabetes who did not work a night shift within the last 2 years and who did not cross time zones within the last 6 months of this study. Patients were excluded in cases of steroid use, insulin treatment, impaired renal or liver function, diabetic retinopathy, and cardiovascular diseases. The patients habitually woke up between 0600 h and 0800 h and went to sleep between 2200 h and 2400 h. The study protocol was conformed to the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Osaka Prefecture University and Kyoto Women's University, and was registered at Clinical Trials gov. (UMIN 000015108). All patients gave written informed consent to participate in the study and for the study's findings to be published.

2.2. Study design

This was a randomized, open-label, cross-over, within-patient clinical trial. Two weeks prior to the study, the patients underwent an examination to obtain their anthropometric measurements with blood sampling for fasting plasma glucose, and for HbA1c after an overnight fast. The patients' characteristics such as medical history and current medication use were also recorded.

During the test period, each patient wore a continuous glucose monitor (CGM, iPro2, Medtronic Japan, Tokyo) for 5 days and consumed identical test meals for 3 consecutive days from the second to the fourth day (Fig. 1). On the first day, each patient arrived at the clinic at 1600 h, and the patient was fitted with a CGM by a clinic nurse. The patients were also provided a self-monitoring blood glucose device (SMBG, Sanwa Kagaku Kenkyusyo, Aichi, Japan) and were instructed to perform the required sensor calibration procedure four times daily. Each patient consumed the identical test meals of breakfast at 0800 h, lunch at 1300 h, and dinner at 2100 h or a divided dinner (tomato and rice at 1800 h, and the spinach and the main dish at 2100 h) on the second or the fourth day, and dinner at 1800 h on the third day at home.

According to the randomized cross-over design, the patients were assigned by dietitians at the clinic wherein they consumed either the divided dinner or the dinner at 2100 h on the second or fourth day. During the study period, the patients were instructed 24-h food record and a 24-h 4 to 5-point SMBG profile (pre-breakfast, lunch, dinner and bedtime readings). Compliance was explained by the face to face meeting individually before and the first day of the study and reinforced with a phone call during the study period by the dietitians of the clinic. On the fifth day, patients returned to the clinic at 1100 h, the CGM was removed, and its data were uploaded and stored electronically.

The daily glucose parameters were compared within-patient for the 3 days of the consumption of the identical dinner at different times. The mean plasma glucose and standard deviation glucose were calculated from 0800 to 0800 h in the next morning. The incremental area under the curves (IAUC) for glucose of 2300–0800 h were calculated by the trapezoidal method above the baseline value for glucose at 1800 h. The incremental glucose peaks (IGPs) were calculated as the maximal blood glucose excursion from the fasting value over the 5-h postprandial period. The mean amplitude of glycemic excursions (MAGE) were calculated from 0800 h to 0800 h in the next morning as described [18].

2.3. Test meals

Patients consumed an identical breakfast, lunch, and dinner by the test meals for 3 days during the test periods at home (Table 1). The test meals, which consisted of boiled white rice, white bread, milk, vegetable, and frozen lunch boxes of gluten-meat steak and fried fish with vegetable (Tokatsu Foods, Yokohama, Japan), had the same macronutrient content and composition within-patient in 3 study days. The composition and nutritional content of the test meals were analyzed by computer software (Microsoft Excel Eiyokun for Window Ver.7.0, Kenpakusya, Tokyo). The test meals were adjusted to meet the caloric requirement of each patient, calculated by 27 kcal/kg/day, by adjusting the amount of carbohydrate with the mean of a sample population prescribed a 1570 kcal per day. The frozen lunch boxes of gluten-meat steak and fried fish with vegetable were provided by the research group, and rice, bread, milk, and other vegetable were prepared by the patients according to the study broche made for each patient by the dietitians. Each patient was indicated to measure all food precisely and record the amount and time of every meal. The patients consumed the first dish of vegetables for 5 min, then the main dish for 5 min, and rice/bread for 5 min in their entirety within 15 min each test meal time. The records of food amount, meal time, and blood glucose values obtained by SMBG of each patient were col-

lected and assessed the compliance of the study protocol by the dietitians. The patients were asked to avoid alcohol and excessive physical activity 2 days preceding the study day and during the study period. Unrestricted amounts of water, green tea, tea, and coffee were permitted to the patients.

2.4. Measurements

Fasting blood samples were collected in the morning after an overnight fast from all patients 2 weeks prior to the study. Fasting plasma glucose was measured by standard laboratory methods. HbA1c levels were determined by a latex cohesion method (JCA-BM2250, Kyowa Medex, Tokyo).

2.5. Statistical analyses

Data are reported as mean ± standard error of the mean (SEM) unless otherwise stated. The primary outcome was the IAUC for glucose, and the secondary outcomes were the IGP and the MAGE. If Friedman's test revealed significant effects for parameters ($p < 0.05$), we performed a paired comparison by Wilcoxon matched-pairs signed rank test followed by post hoc Bonferroni's inequality ($p < 0.017$). The sample size was calculated based on the primary outcome of the IAUC for glucose. Since no data are available on the size effect of meal timing on the IAUC for glucose in patients with type 2 diabetes, we referred to a study of food order [12]. According to that study, a sample size of 7 patients was calculated to have at least 90% power. To allow for discontinuation, 16 patients were recruited. All analyses were performed with SPSS Statistics (ver. 22: SPSS Japan, Tokyo).

3. Results

Sixteen patients enrolled the study and all participants completed the study protocol. The characteristics of the patients are described in Table 2. Six patients were controlled by diet only, and the other 10 patients were taking oral hypoglycemic agents. Four patients were taking antihypertensive medication, and 8 patients were taking lipid-lowering medication. The patients were asked to maintain all medications at their pre-study doses during the study period. The patients who had medication in the evening took their medicine around 1800 h, 2100 h, and 1800 h, in the dinner at 1800 h, the dinner at 2100 h, and the divided dinner, respectively, when they took high carbohydrate.

The plasma glucose and HbA1c levels were not significantly different between the patients who were and were not on oral hypoglycemic agents ($p > 0.05$). All patients woke up between 0600 h to 0700 h and went to bed between 2300 h and 2400 h during the study period.

The plasma glucose levels before breakfast and lunch did not differ significantly among the dinner at 1800 h, the dinner at 2100 h, and the divided dinner, however, the plasma glucose level at 2100 h in the dinner at 2100 h was lower compared to that at 1800 h in the dinner at 1800 h (Table 3).

Fig. 2 demonstrates that the postprandial hyperglycemia after the patients consumed the late dinner was sustained throughout the night in the dinner at 2100 h. The values of mean plasma glucose, the IGP after dinner, and the IAUC 2300–0800 h were significantly higher for the dinner at 2100 h compared to those for the dinner at 1800 h (Table 3). The value of MAGE for the dinner at 2100 h was tended to

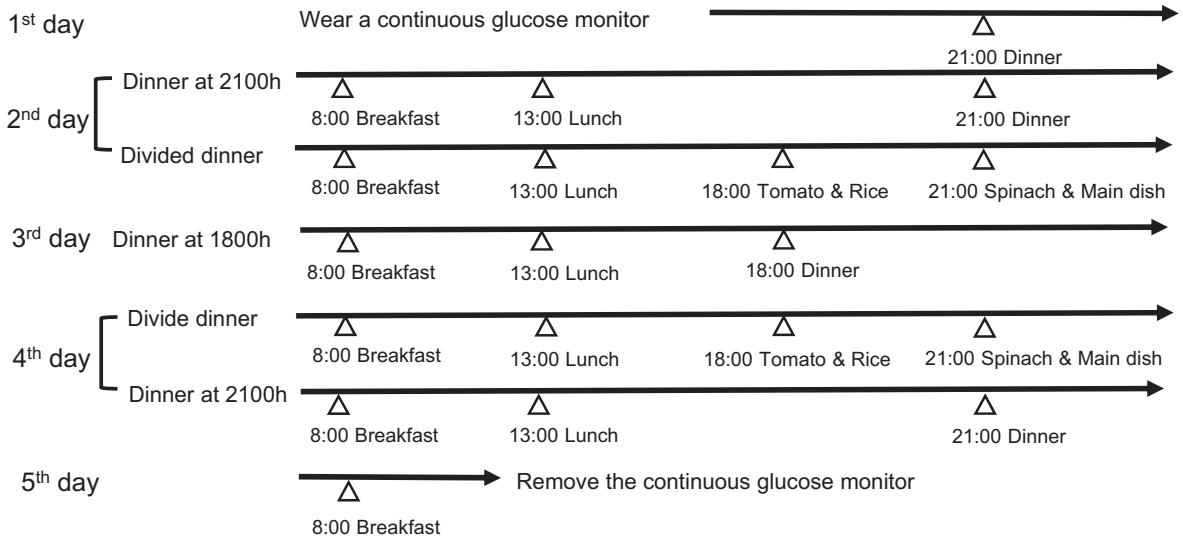

Fig. 1 – Schematic illustration of the study. During the test period, each patient wore a CGM for 5 days and consumed identical test meals for 3 consecutive days from the second to the fourth day. Each patient consumed the identical test meals of breakfast at 0800 h, lunch at 1300 h, and dinner at 2100 h or the divided dinner (tomatoes and rice at 1800 h and the spinach and the main dish at 2100 h) on the second or the fourth day, and dinner at 1800 h on the third day. On the fifth day the CGM was removed. According to the randomized cross-over design, the patients were assigned wherein they consumed either the divided dinner or the dinner at 2100 h on the second or the fourth day.

Table 1 – The composition and macro-nutritional contents of the test meals.

		Energy (kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	Fiber (g)	Detail content
Breakfast		407	17.8	11.9	58.9	5.7	White bread 90 g, tomato 100 g, broccoli 60 g, milk 200 g, strawberry jam (sugar free) 13 g
Lunch		539	22.9	11.2	82.4	7.7	Boiled white rice 160 g, Frozen lunch box of fried fish with vegetable, tomato 100 g, spinach 80 g
Dinner		624	22.8	20.1	86.6	7.6	
Divided dinner	at 1800 h	(271)	(4.5)	(0.6)	(60.4)	(1.5)	Boiled white rice 160 g, seasoned seaweed, tomato 100 g
	at 2100 h	(353)	(18.3)	(19.6)	(26.2)	(6.1)	Frozen lunch box of gluten-meat steak with vegetable, spinach 80 g with fried tofu 15 g
Total		1570	63.5	43.2	227.9	21.0	

be higher than that for the dinner at 1800 h, although there was no statistical difference between 2 days.

On the other hand, the values of the IGP after dinner, the IAUC 2300–0800 h, and the MAGE for the divided dinner were all significantly ameliorated compared to those for the dinner at 2100 h (Table 3). The value of mean plasma glucose for the divided dinner was ameliorated compared to that for the dinner at 2100 h, although there was no significant difference between 2 days.

4. Discussion

We observed that (1) the patients' consumption of the late-night-dinner was associated with postprandial hyperglycemia, and (2) their consumption of the divided dinner reduced postprandial hyperglycemia and the MAGE as reflected by the decrease of the IGP. Remarkably, the IAUC for the glucose at 2300 to 0800 h was approx. 4.5 times higher in the late-night-dinner compared to those in the divided dinner or the early-evening-dinner. Therefore the reduction of postprandial hyperglycemia by consuming the divided dinner can be a practical strategy for patients with type 2 diabetes who consume dinner late at night.

The higher postprandial glucose levels through the night observed in the late-night-dinner might be influenced by the circadian clock on glucose metabolism. Feeding versus fasting is an important key to change transcript levels and the circadian phase of peripheral clock genes and genes related to glucose metabolism. Morris et al. [19] reported that diet-induced thermogenesis (DIT) was 40–50% lower at night than in the morning in healthy adults. As a result, disorder of the circadian rhythm leads to insulin resistance, hypertension, and other metabolic responses [20–22]. The circadian misalignment of meal timing as a result of late-night-dinners and longer fasting hours before dinner may have augmented postprandial hyperglycemia throughout the night in the dinner at 2100 h of the present study. The consumption of a divided dinner might be particularly effective for shift and night workers to lower the risk of obesity and metabolic syndrome and to prevent cardiovascular diseases, because some of the increased risk of diseases in shift workers may be associated with diet or meal timing [23,24].

The elevation of plasma free fatty acid (FFA) level at 2100 h of the dinner at 2100 h would be one of the reasons for the increasing postprandial glucose or insulin level during the night after consuming the dinner at 2100 h which we identified in some of the patients (Dinner at 2100 h; 0.69 ± 0.10 vs. Dinner at 1800 h; 0.33 ± 0.06 mmol/L, $p = 0.070$ by Wilcoxon matched-pairs signed rank test followed by post hoc Bonferroni's inequality, $n = 8$). Because the acute elevation of FFA levels is associated with hepatic insulin resistance and increasing hepatic glucose production at 4–6 h after a meal [25–27].

On the other hand, the one of the reasons for the reduction of postprandial glucose levels through the night observed in the divided dinner can be explained by the decrease of the meal size and the amount of carbohydrate in each meal. The amount of carbohydrate in the first meal consumed at 1800 h was about 70% of the whole dinner, and about 30% of the second meal at 2100 in the divided dinner. Therefore, when the patients consumed the vegetable and the main dish at 2100 h the blood glucose level barely increased and decreased to the baseline after 3 h.

Alternatively, the reduction of the postprandial glucose excursion by the consumption of the divided dinner may be explained by the second meal phenomenon. The glucose level increased when the vegetable and the rice were consumed at 1800 h while the increase of the postprandial glucose level was slight after consumption of the vegetable and the main dish at 2100 h in the divided dinner. This has been explained by enhanced β-cell responsiveness at the second meal as induced by the first meal, based on the findings that the first and second phases of insulin release are influenced by β-cell memory, and the insulin release is enhanced by previous glucose exposure [28–31]. Therefore, consuming a divided dinner could be effective to suppress the large glycemic excursion during the whole night in patients with type 2 diabetes.

In this study, we investigated the acute effect of late-night-dinner and divided dinner on postprandial glucose levels in patients with type 2 diabetes using CGM. However, this study has some limitations. First, some patients were taking oral hypoglycemic agents, antihypertensive drugs, and lipid-lowering medicine in this study. However, this study was a cross-over within-patient trial, thus medication

Table 2 – Characteristics of the patients with type 2 diabetes.

	$n = 16$
Male/female	8/8
Age (years)	70.3 ± 5.6
Duration of diabetes (years)	13.7 ± 10.9
Body weight (kg)	60.2 ± 10.8
BMI (kg/m^2)	22.8 ± 2.7
HbA1c [(%) mmol/mol]	7.2 ± 0.6 (55 ± 6.6)
Fasting plasma glucose (mmol/L)	7.2 ± 1.1
Systolic blood pressure (mmHg)	142 ± 14
Diastolic blood pressure (mmHg)	72 ± 11
Diet therapy only	6
Oral glucose lowering medication	10
Sulfonylurea	8
Dipeptidyl peptidase-IV (DPP4) inhibitor	6
α-glucosidase inhibitor	3
Metformin	3
Mitiglinide	1
Thiazolidinedione	1
Antihypertensive medication	4
Lipid-lowering medication	8

Data are expressed as mean ± SD or *n*.

Table 3 – Characteristics of glycemic excursion in the patients with type 2 diabetes.

	Dinner at 1800 h ($n = 16$)	Dinner at 2100 h ($n = 16$)	Divided dinner ($n = 16$)
Mean plasma glucose (mmol/L)	8.11 ± 0.35	8.72 ± 0.45*	8.09 ± 0.40
Standard deviation plasma glucose (mmol/L)	1.82 ± 0.18	2.21 ± 0.20	1.83 ± 0.16
MAGE (mmol/L)	5.35 ± 0.51	6.99 ± 0.60	5.33 ± 0.41†
Pre-dinner plasma glucose (mmol/L)	7.91 ± 0.43	6.45 ± 0.42*	7.31 ± 0.34
IGP after dinner (mmol/L)	3.09 ± 0.62	6.78 ± 0.79**	3.75 ± 0.58†
IAUC for glucose of 2300–0800 h (mmol/L × min)	147 ± 63	644 ± 156*	142 ± 60†

Data are mean ± SEM. MAGE; mean amplitude of glycemic excursion, IGP; incremental glucose peak, IAUC; Incremental area under the curve. The mean plasma glucose, standard deviation plasma glucose, and MAGE were calculated from 0800 to 0800 h. Pre-dinner plasma glucose were measured at 1800 h for dinner at 1800 h and divided dinner, and at 2100 h for dinner at 2100 h. The IGPs after dinner were calculated as the maximal blood glucose excursion from the fasting value over the 5-h postprandial period. The IAUCs for glucose of 2300–0800 h were calculated by the trapezoidal method above the baseline value for glucose at 1800 h.

Dinner at 2100 h vs. Dinner at 1800 h; * $p < 0.01$, ** $p < 0.001$. Dinner at 2100 h vs. Divided dinner; † $p < 0.01$.

Second, the study population consisted of Japanese men and women, therefore it is uncertain whether these findings are generalized in other ethnic groups. Lastly, we assume both dividing the dinner and nutritional composition of the dinner might affect the postprandial glucose levels in the dividing dinner, although we did not perform "just dividing dinner with same nutritional composition" nor "reverse the nutritional composition of 1800 h and 2100 h". Because we designed to divide dinner as high carbohydrate diet at 1800 h and high protein, fat and fiber diet at 2100 h in this study for patients to adopt this beneficial effect in their lifestyle easily.

To the best of our knowledge, this is the first study to assess the effect of late-night-dinner and a divided dinner on postprandial glucose responses in patients with type 2 diabetes. Not only the amount of total energy or carbohydrate but also the timing of meal consumption are thus important factors for diet therapy. However, our study was restricted to patients with type 2 diabetes and additional investigations are required to clarify the exact mechanism of meal timing in individuals with and without type 2 diabetes.

5. Conclusions

Our study is the first to show that in patients with type 2 diabetes, (1) consuming a late-night-dinner led to postprandial hyperglycemia, and (2) this postprandial hyperglycemia after the late-night-dinner can be ameliorated by consuming a divided dinner. The strategy of consuming a divided dinner

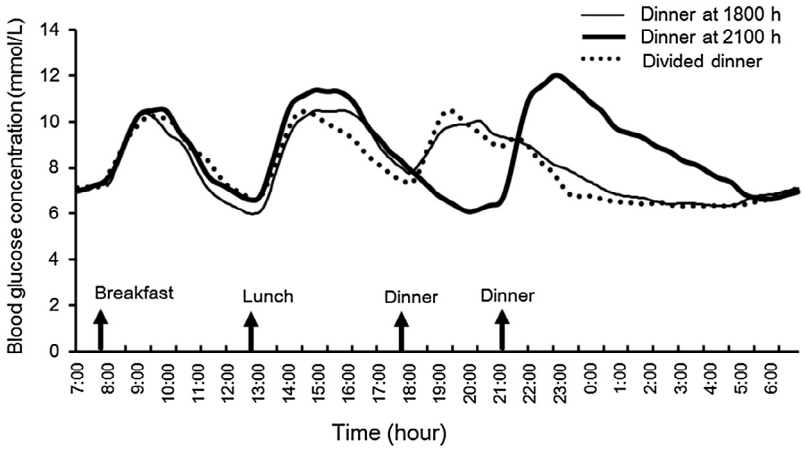

Fig. 2 – The mean of the daily blood glucose profiles by CGM in the patients with type 2 diabetes (*n* = 16). Thin line: dinner at 1800 h. Bold line: dinner at 2100 h. Dotted line: divided dinner. Each patient consumed the dinner at 2100 h or a divided dinner (tomato and rice at 1800 h, and the spinach and the main dish at 2100 h) on the second or the fourth day, and dinner at 1800 h on the third day at home.

might provide a crucial contribution to the prevention of diabetic complications in patients with type 2 diabetes who cannot avoid eating late at night.

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Author contributions

SI designed the study, conducted the experiments, performed the data analysis, and wrote the article. SK recruited and treated all study patients, conducted the experiments, and contributed to the writing of the article. YH conducted the experiments, treated all study patients, performed the data analysis and contributed to the writing of the article. CY conducted the experiments and contributed to data collection. TM, MT, and NO contributed to the discussion and reviewed the article. MF conducted the experiments, performed the data analysis, and contributed to the writing of the article. All authors approved the final version of the article. SI and SK are guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior presentation

This study was presented at the 9th World Congress on Prevention of Diabetes and its complications, Atlanta, USA, 2–4 December 2016.

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