ORIGINAL

Late-night-dinner is associated with poor glycemic control in people with type 2 diabetes: The KAMOGAWA-DM cohort study

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Abstract. Skipping breakfast or irregular breakfast is associated with poor glycemic control. However, a relationship between the timing of dinner and glycemic control in people with type 2 diabetes remains indefinite. Therefore, we investigated the relationship between late-night-dinner and glycemic control in people with type 2 diabetes. We performed questionnaire survey for lifestyle factors in this cross-sectional study. We defined having dinner later than eight pm as late-night-dinner. We examined the differences in clinical and metabolic parameters between those who have late-night-dinner and those who do not have. We also examined the relationship between late-night-dinner and HbA1c, using multiple regression analysis. Ninety-five people (23.2%) had a late-night-dinner, among 409 people with type 2 diabetes. Metabolic parameters (mean (SD) or median (interquartile range)) of people with late-night-dinner were worse than those of without, including body mass index (BMI) (24.4 (4.0) *vs.* 23.2 (3.4) kg/m^2, *p* = 0.006), triglycerides (1.5 (1.1–2.1) *vs.* 1.2 (0.8–1.7) mmol/L, *p* < 0.001), HDL-cholesterol (1.4 (0.4) *vs.* 1.6 (0.4) mmol/L, *p* = 0.004) and hemoglobin A1c (58.1 (13.3) *vs.* 55.2 (10.2) mmol/mol, (7.5 (1.2) *vs.* 7.2 (0.9) %), *p* = 0.023)). Late-night-dinner (standardized regression coefficient = 0.13, *p* = 0.028) was associated with hemoglobin A1c after adjusting for age, BMI, sex, duration of diabetes, smoking, exercise, alcohol, snacking after dinner, nighttime sleep duration, time from dinner to bedtime, skipping breakfast, and medication for diabetes. Late-night-dinner is independently associated with poor glycemic control in people with type 2 diabetes.

Key words: Nutrition and diet, Obesity, Lifestyle, Type 2 diabetes, Late-night-dinner

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LIFESTYLE CHANGE, which has become diverse and irregular, recently, is the cause of change in food consumption patterns [1, 2]. Energy regulation is associated with the circadian clock in molecular level and food intake has important role in metabolic parameters, through circadian clock [3-5]. Irregularity of meal pattern is now reported as a new potential risk factor for metabolic syndrome, diabetes and cardiovascular disease [6, 7]. In fact, irregular and skipping breakfast increase the risk of obesity, metabolic syndrome and poor glycemic control [8].

Meanwhile, in Japan, dinner is the main meal of the day and the greatest energy is intake by dinner [9]. About two-fifths Japanese eat dinner from 2000 to 2400 h [10]. It has been reported that late-night-dinner has associated with obesity, metabolic syndrome and hyperglycemia in general population [11-14]. Besides, it is reported that the risks of metabolic syndrome, diabetes and insulin resistance in the people with having high calorie at dinner were higher than those in the people with having high calorie at breakfast [15]. Another study

showed that the evening chronotype was risk of diabetes and metabolic syndromes [16]. In fact, it is well known that night shift work is a risk of incident diabetes [17, 18]. Thus, dinner timing is an important issue in the clinical setting. However, little is known about the relationship between late-night-dinner and glycemic control in people with type 2 diabetes. Therefore, in this cross-sectional study, we examined the relationship between late-night-dinner and glycemic control of people with type 2 diabetes.

Materials and Methods

Patients and study design

The KAMOGAWA-DM cohort study is an ongoing cohort study of people with diabetes. The purpose of this cohort study, which was started from 2014, is to clarify the natural history of people with diabetes. We served the results of the medical data into a database after giving informed consent and keeping personal identifiable information secret. The inclusion criteria of this cross-sectional study was the outpatient with type 2 diabetes, diagnosed by a physician, at the Kyoto Prefectural University of Medicine, from January 2014 to January 2016. The people under steroid treatment, after a renal transplantation, after a liver transplantation, with severe renal dysfunction (estimated Glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2) [19], shift workers who work at night and the people who did not have dinner were excluded. In addition, the people, whose data (blood biochemical examinations or questionnaires) were incomplete, were also excluded. Approval for this study was obtained from the Ethics Committee of Kyoto Prefectural University of Medicine (No. RBMR-E-466-1).

Questionnaire and measurements

We evaluated lifestyle factors by a questionnaire survey. As for exercise status, the people who performed any kind of sports at least once a week regularly on the questionnaire were defined as regular exercisers [20]. As for alcohol, the people who drank alcohol daily were defined as alcohol drinker. As for smoking, smoking status was defined by current use of cigarette [21, 22]. Skipping breakfast was determined based on a negative answer to the question: "Do you have breakfast regularly?" In addition, we asked whether having daily dinner or not and the time of dinner. When the answer was having daily dinner and the dinner time was later than eight pm [23], we defined it as late-night-dinner. About

status of snacking after dinner, we defined it as having daily snacking after dinner by the answer of the regular snacking time and dinner time. Nighttime sleep duration was evaluated by the answer of the regular bedtime and the regular get up time, and likewise the time from dinner to bedtime was evaluated by the answer of the regular bedtime and the dinner time.

Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Overweight and obesity status were defined as BMI over 23 kg/m^2 and over 25 kg/m^2 [24-26]. Venous blood after an overnight fast were collected and then we measured the levels of various factors, including fasting plasma glucose, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyltransferase, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, uric acid and creatinine. Hemoglobin A1c was assayed using high-performance liquid chromatography and was expressed as a National Glycohemoglobin Standardization Program unit. Glomerular filtration rate (GFR) was estimated using the Japanese Society of Nephrology equation: estimated GFR (eGFR) (mL/min/1.73 m^2) = $194 \times$ serum creatinine$^{-1.094} \times$ age$^{-0.287}$ ($\times 0.739$ for women) [27].

We also investigated the diabetic medications and categorized as follows: insulin, insulin secretagogues, insulin sensitizers and nutrient load reducers [28]. Insulin secretagogues included sulfonylureas, glinides, dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonist; insulin sensitizers included pioglitazone and metformin; and nutrient load reducers included α-glucosidase inhibitors and sodium-glucose cotransporter inhibitors [28]. Moreover, we also investigated the medications affecting to lipids and BMI, including statins, fibrates, ezetimibe and eicosapentaenoic acid for lipids and diuretics for BMI.

Statistical analysis

We used JMP version 12.0 software (SAS Institute, Cary, NC, USA) for statistical analyses and we considered $p < 0.05$ as statistically significant. We calculated mean, median and frequencies of potential confounding variables. The people were divided into two groups according to late-night-dinner or not. Continuous variables were presented as the mean (standard deviation (SD)) or median (interquartile range), and Student's t-test or Mann-Whitney U test was used for evaluating statistical significance of differences. Categorical variables were presented as percent (number) and Chi-square
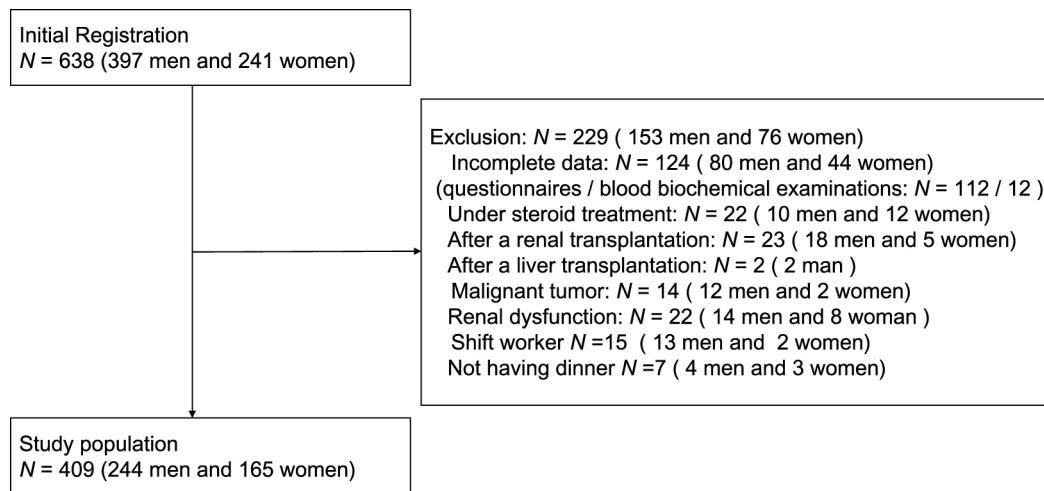
Fig. 1 Inclusion and exclusion of the study participants

test was used for evaluating statistical significance of differences between groups.

To investigate the relationship between various factors and hemoglobin A1c, we performed the multiple regression analysis and the following factors, which are including the well-known variates to affect HbA1c [29-31], were considered simultaneously as independent variables for multiple regression analysis: sex, BMI, age, duration of diabetes, nighttime sleep duration, time from dinner to bedtime, exercise, smoking, snacking after dinner, alcohol drinking, skipping breakfast, and usage of insulin treatment, insulin secretagogues, insulin sensitizers and nutrient load reducers. We also performed the multiple regression analysis to investigate the relationship between late-night-dinner and Log TG, HDL cholesterol or BMI.

Results

In this study, 638 people (397 men and 241 women) with type 2 diabetes were included. Among them, 229 people (153 men and 76 women) were excluded; 112 people who were incomplete with questionnaires, and 12 people who were with blood biochemical examinations were included. Thus, the study population was 409 people (244 men and 165 women) (Fig. 1).

Clinical characteristics of study participants are shown in Table 1. The average (SD) of age and duration of diabetes were 68.3 (10.9) years and 13.6 (10.1) years. In this study population, 95 people (23.2%) had late-night-dinner, 17 people (4.2%) skipped breakfast, and 22 peo-

ple (5.3%) had regularly snacking after dinner.

Metabolic parameters, including BMI, blood pressure, HbA1c, total cholesterol, triglycerides, alanine aminotransferase and gamma-glutamyltransferase, of people with late-night-dinner were higher than those of people without and HDL cholesterol of people with late-night-dinner was lower than that of people without (Table 1).

The ratio of exerciser in people with late-night-dinner was lower than that in people without ($p = 0.015$) and the ratio of overweight, obesity and skipping breakfast in people with late-night-dinner was higher than that in people without ($p = 0.003$) (Table 1). In addition, we also investigated the dose and frequency of drug including glimepiride ($n = 130$), metformin ($n = 139$), sitagliptin ($n = 128$) and voglibose ($n = 24$), which were mainly prescribed in each class, and insulin ($n = 87$), and we compered them between people with and without late-night-dinner. Among them, average dose of insulin was solely different between people with and without late-night-dinner (25.9 (12.8) *vs.* 18.9 (11.9) units, $p = 0.027$).

Multiple regression analysis showed that late-night-dinner (standardized regression coefficient = 0.131, $p = 0.026$) was associated with HbA1c after adjusting covariates (Table 2). In addition to that, dinner time (as a continuous variable) was associated with HbA1c (standardized regression coefficient = 0.141, $p = 0.029$) after adjusting covariates. Furthermore, late-night-dinner was associated with Log TG (standardized regression coefficient = 0.116, $p = 0.039$) after adjusting for sex, BMI, age, duration of diabetes, nighttime sleep duration, time from dinner to bedtime, exercise, smoking, snacking

Table 1   Clinical characteristics of study patients

	Total	Late-night-dinner (–)	Late-night-dinner (+)	*p*
N	409	314	95	—
Men/Women (*n*)	244/165	176/138	68/27	0.007
Age (year)	68.3 (10.9)	70.6 (9.3)	60.7 (12.3)	<0.001
Duration of diabetes (year)	13.6 (10.1)	13.9 (10.1)	12.5 (10.2)	0.156
Body mass index (kg/m^2)	23.5 (3.6)	23.2 (3.4)	24.4 (4.0)	0.006
Non-overweight/Overweight/Obesity (*n*)	180/117/112	151/86/77	29/31/35	0.007
Systolic blood pressure (mmHg)	129.7 (15.0)	129.5 (15.3)	130.6 (14.1)	0.497
Diastolic blood pressure (mmHg)	71.8 (11.5)	70.5 (10.9)	76.1 (12.2)	<0.001
Hemoglobin A1c (mmol/mol)	55.9 (11.0)	55.2 (10.2)	58.1 (13.3)	0.023
Hemoglobin A1c (%)	7.3 (1.0)	7.2 (0.9)	7.5 (1.2)	0.023
Fasting plasma glucose (mmol/L)	8.1 (2.5)	8.1 (2.4)	8.3 (2.7)	0.560
Total cholesterol (mmol/L)	4.8 (0.8)	4.7 (0.8)	5.0 (1.0)	0.011
Triglycerides (mmol/L)	1.2 (0.9–1.7)	1.2 (0.8–1.7)	1.5 (1.1–2.1)	<0.001
HDL cholesterol (mmol/L)	1.5 (0.4)	1.6 (0.4)	1.4 (0.4)	0.004
Aspartate aminotransferase (IU/L)	25.6 (13.5)	25.1 (11.8)	27.0 (17.9)	0.851
Alanine aminotransferase (IU/L)	24.4 (18.7)	22.7 (15.9)	29.7 (25.2)	0.002
gamma-glutamyltransferase (IU/L)	25 (18–41)	24 (17–37)	30 (21–52)	0.001
Creatinine (μmol/L)	70.6 (21.7)	70.4 (22.1)	71.3 (20.2)	0.731
eGFR (mL/min/1.73 m^2)	71.7 (19.1)	70.5 (18.7)	75.9 (19.9)	0.022
Uric acid (μmol/L)	313 (76)	311 (77)	319 (76)	0.427
Nighttime sleep duration (hour)	7.3 (1.4)	7.5 (1.4)	6.8 (1.3)	<0.001
Time from dinner to bedtime (hour)	4.3 (1.3)	4.5 (1.2)	3.5 (1.2)	<0.001
Exercise (–/+)	188/221	134/180	54/41	0.015
Smoking (–/+)	357/52	278/36	79/16	0.168
Alcohol drinking (–/+)	323/86	248/66	75/20	0.994
Snacking after dinner (–/+)	387/22	297/17	90/5	0.955
Skipping breakfast (–/+)	392/17	306/8	86/9	0.003
Late-night-dinner (–/+)	314/95	—	—	—
Insulin treatment (–/+)	317/92	241/73	76/19	0.506
Insulin dose (units/ day)	20.4 (12.4)	18.9 (11.9)	25.9 (12.8)	0.027
Diuretics (–/+)	345/64	261/53	84/11	0.213
Statins (–/+)	219/190	166/148	53/42	0.617
Fibrates (–/+)	385/24	300/14	85/10	0.028
Ezetimibe (–/+)	390/19	297/17	93/2	0.179
Eicosapentaenoic acid (–/+)	398/11	308/6	90/5	0.077
Insulin secretagogues (–/+)	100/309	79/235	21/74	0.544
Sulfonylureas	235/174	177/137	58/37	0.419
Glinides	376/33	287/27	89/6	0.474
Dipeptidyl peptidase-4 inhibitors	172/237	132/182	40/55	0.991
Glucagon-like peptide-1 receptor agonist	387/22	302/12	85/10	0.011
Insulin sensitizers (–/+)	249/160	198/116	51/44	0.101
Pioglitazone	378/31	287/27	91/4	0.157
Metformin	266/143	214/100	52/43	0.016
Nutrient load reducers (–/+)	335/74	255/59	80/15	0.506
α-glucosidase inhibitors	357/52	274/40	83/12	0.978
Sodium-glucose cotransporter inhibitors	385/24	294/20	91/4	0.433

Data are expressed as mean (SD), median (interquartile range) or number. HDL, High-density lipoprotein; eGFR, estimated glomerular filtration rate. The difference between groups was analyzed by Student's *t*-test, Mann-Whitney U test or Chi-square test.

Table 2 Multiple regression analysis on Hemoglobin A1c (mmol/mol)

	standardized regression coefficient	p
Sex	−0.046	0.365
Age (year)	0.038	0.506
Duration of diabetes (year)	0.165	0.002
Body mass index (kg/m²)	0.185	0.000
Exercise	−0.029	0.549
Smoking	0.034	0.478
Alcohol drinking	−0.026	0.605
Skipping breakfast	0.032	0.516
Snacking after dinner	−0.035	0.464
Insulin treatment	0.130	0.012
Insulin secretagogues	0.103	0.035
Insulin sensitizers	0.041	0.403
Nutrient load reducers	0.076	0.119
Time from dinner to bedtime, hour	0.092	0.131
Nighttime sleep duration, hour	−0.047	0.413
Late-night-dinner	0.129	0.028

Sex was defined as women (=0) or men (=1); exercise status was defined as non-regular exerciser (=0) or regular exerciser (=1); smoking status was defined as non-smoker (=0) or smoker (=1); alcohol drinking was defined as non-regular alcohol consumer (=0) or regular alcohol consumer (=1); skipping breakfast was defined as non-skipper (=0) or skipper (=1); snacking after dinner was defined as not having daily snacking after dinner (=0) or having (=1); insulin treatment, insulin secretagogues, insulin sensitizers and nutrient load reducers were defined as without (=0) or with (=1). Late-night-dinner was determined by the dinner time. We defined the late-night-dinner which is having dinner later than 20:00 as without (=0) or with (=1).

after dinner, alcohol drinking, skipping breakfast, and usage of statins, fibrates, ezetimibe and eicosapentaenoic acid for lipids, whereas, late-night-dinner was not associated with HDL cholesterol (standardized regression coefficient = −0.056, p = 0.312). Moreover, late-night-dinner was not associated with BMI (standardized regression coefficient = 0.080, p = 0.155) after adjusting for sex, age, duration of diabetes, nighttime sleep duration, time from dinner to bedtime, exercise, smoking, snacking after dinner, alcohol drinking, skipping breakfast and diuretics affecting to BMI.

Discussion

We demonstrated that late-night-dinner was independently associated with poor glycemic control in people with type 2 diabetes. In addition, we also demonstrated that the metabolic parameters, especially TG, of people with late-night-dinner were worse than those of people without. It has been reported that late-night-dinner is associated with poor cardiometabolic profiles in general population [12, 32]. However, the relationship between late-night-dinner and glycemic control in people with type 2 diabetes is not reported. This is the first study to clarify the relationship between late-night-dinner and glycemic control in people with type 2 diabetes.

One of the possible explanations why late-night-dinner is associated with poor glycemic control is that late-night-dinner prolongs the postprandial glucose spike for a long time [33]. In fact, during the night, decreasing of glucose tolerance and insulin sensitivity are shown [34]. Another possible explanations is the effect of circadian rhythms on glucose metabolism. It is well known that many physiologically and nutritionally processes have the circadian rhythms in human body [35]. Nutrition factors, such as food intake, appetite and digestion, have an effect on circadian patterns [36]. Food intake modulates the circadian rhythms, especially in liver and intestine [37, 38] and misalignment of circadian rhythm leads to insulin resistance and diabetes [39, 40]. In fact, skipping breakfast, one of the irregular eating, is associated with metabolic syndrome, diabetes and cardiovascular disease [6, 7]. Moreover, late-night-dinner might be concerned with poor glycemic control *via* reduced diet-induced thermogenesis (DIT). Because, DIT is about 10% of total energy expenditure, and it is the greatest in the morning and declines toward late at night [41]. Taking together, late-night-dinner is associated with poor glycemic control.

We also demonstrated that duration of diabetes, insulin treatment and usage of insulin secretagogues were also associated with poor glycemic control in this study. It has been reported that usage of insulin or number of antidiabetic medications was associated with poor glycemic control [29, 30]. In fact, usage of insulin secretagogues was correlated with number of antidiabetic medications (p < 0.001 by Student's *t*-test) in this study. Medication is the important treatment for type 2 diabetes, but diet and exercise therapies are the fundamental treatments for patients with type 2 diabetes [42]. Therefore, we often fail to adjust HbA1c by modification of medication, including due to poor adherence of medication [43],

although the details of adherence of medication in people with diabetes is not clarified.

In this study, we demonstrated that late-night-dinner was a risk of poor glycemic control. Thus, to improve glycemic control, having dinner before eight pm is needed. However, it is difficult for all people to have dinner before eight pm. A recent study demonstrated that dividing consumption of late-night-dinner can suppress postprandial hyperglycemia [44].

This study has some limitations. First, we evaluated dinner time and lifestyle factors using self-reports. There is a potential bias, because there is a possibility that people may report generally desirable answers which are considered to be healthy. In addition, the validity of a questionnaire for late-night-dinner is not enough. However, many studies have defined nighttime dinners using a questionnaire including answers to dinner time [12, 45, 46]. Likewise, we assessed late-night-dinner as the major observation by the time obtained from questionnaire. Second, we did not have the detail data of the meal. It is reported that the late-night-dinner is less satiating and can become the cause of overeating [47]. Therefore, the overeating as a result of late-night-dinner might have affected the poor glycemic control. However, even with the same meal contents, consuming in late-night-dinner lead to postprandial hyperglycemia [44]. Furthermore, it is reported that there is a significant correlation between skipping breakfast and late-night-dinner [48]. So, skipping breakfast might affect the result on this study. In fact, the proportion of skipping breakfast in people with late-night-dinner was higher than that in people without ($p = 0.003$) in this study. However, when we used a skipping breakfast as a covariate in this study, the effect of late-night-dinner was independently associated with worse HbA1c from skipping breakfast. In addition, the glycemic control of people with late-night-dinner were worse than that of people without (7.43% *vs.* 7.20%, $p = 0.047$ by Chi-square test), even when we excluded people who regularly skipped breakfast. Thus, late-night-dinner itself is associated with the poor glycemic control. Third, medications for diabetes might affect the results of this study, although we handled the medications for diabetes as covariates to correct the effect of medications in this study. Lastly, in this study, people are Japanese only. Therefore, the generalizability of our study to non-Japanese populations is uncertain.

In conclusion, this cross-sectional study demonstrates, for the first time, late-night-dinner is associated with poor glycemic control in people with type 2 diabetes.

Thus, we should focus more on the timing of dinner for management of people with type 2 diabetes.

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