Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Association between postprandial hyperglycemia at clinic visits and all-cause and cancer mortality in patients with type 2 diabetes: A long-term historical cohort study in Japan

Toshiko Takao [a,*], *Kazuyuki Takahashi* [a], *Machi Suka* [b], *Nobumi Suzuki* [c], *Hiroyuki Yanagisawa* [b]

[a] *Division of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan*
[b] *Department of Public Health and Environmental Medicine, The Jikei University School of Medicine, Tokyo, Japan*
[c] *Division of Gastroenterology, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan*

ARTICLE INFO

Article history:
Received 22 August 2018
Received in revised form
13 December 2018
Accepted 4 January 2019
Available online 11 January 2019

Keywords:
All-cause mortality
Cancer mortality
Clinic visit
Postprandial hyperglycemia
Type 2 diabetes

ABSTRACT

Aims: To evaluate the effect of postprandial hyperglycemia at clinic visits on all-cause and cancer mortality independent of glycated hemoglobin (HbA1c) levels in a real-world setting in Japanese patients with type 2 diabetes. We also investigated age at death.
Methods: This historical cohort study included 1582 patients with type 2 diabetes who first visited our clinic from 1995 to 1998 and continued visiting for at least 1 year. The patients were followed up through 2017. Blood glucose levels at 2 h ± 30 min post-breakfast (2h-PBBG) were measured in 926 patients during the first year. The first measurements of 2h-PBBG levels were used as a measure of postprandial hyperglycemia.
Results: A total of 233 patients died. The average age at death (men/women) was 75.6/80.8 years. A total of 139 patients who had 2h-PBBG levels measured died, including 46 deaths from cancer. Multivariate Cox regression analysis showed that 2h-PBBG levels significantly predicted all-cause and cancer mortality independent of HbA1c levels.
Conclusions: Postprandial hyperglycemia at clinic visits may be associated with all-cause and cancer mortality in patients with type 2 diabetes independent of HbA1c levels. As this is a small observational study, further studies are warranted to confirm our findings.

1. Introduction

There is evidence that patients with type 2 diabetes are associated with insulin resistance, hyperinsulinemia, and an increased risk of several site-specific cancers and cancer-related mortality [1,2]. Chronic hyperglycemia as evaluated by measuring glycated hemoglobin (HbA1c) levels correlates with an increased risk of cancer [3]. HbA1c is a biomarker of mean blood glucose concentrations for a prolonged period of time, and not affected by recent meals [4]. The risk of cancer is already increased in the pre-diabetic and normal range of HbA1c levels [3]. Fasting glucose levels are nonlinearly

* Corresponding author at: Division of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, 2-2-6, Nihonbashi Bakurocho, Chuo-ku, Tokyo 103-0002, Japan.
E-mail address: t-takao@asahi-life.or.jp (T. Takao).
https://doi.org/10.1016/j.diabres.2019.01.006
0168-8227/

related to the risk of death [5]. Fasting glucose levels exceeding 100 mg/dL (5.6 mmol/L), but not levels of 70–100 mg/dL (3.9–5.6 mmol/L), are associated with an excess risk of death. However, associations with death from cancer tend to plateau at higher fasting glucose levels [5].

In a general Japanese population who underwent a 75-g oral glucose tolerance test, the risk of death from cancer was significantly higher in subjects with 2-h postload glucose levels of ≥11.1 mmol/L than in those with the lowest level of 6.7 mmol/L [6]. However, the results obtained from people without diabetes cannot be transferred to patients with diabetes. Furthermore, postload glycemia obtained using an oral glucose tolerance test cannot be equated to postprandial glycemia.

Acute glucose excursions rather than sustained hyperglycemia trigger oxidative stress [7,8]. Oxidative stress generates DNA damage [9], increases inflammation [10], and causes vascular endothelial damage, which may contribute to progression of cancer and atherosclerosis. In the clinical setting, an interventional trial in patients with type 2 diabetes after acute myocardial infarction showed no definite proof that targeting postprandial hyperglycemia results in a more beneficial outcome of cardiovascular disease (CVD) [11], except for post-hoc subgroup analysis in older patients [12]. A systematic review of a few observational studies showed that postprandial hyperglycemia was associated with increased all-cause and cardiovascular mortality, the incidence of CVD, and progression of diabetic retinopathy [13]. In our previous observational study in patients with type 2 diabetes, postprandial hyperglycemia was associated with the incidence of CVD and all-cause mortality [14]. To the best of our knowledge, no epidemiological study has examined the relationship between postprandial hyperglycemia and cancer mortality in patients with type 2 diabetes.

According to a report from the Ministry of Health, Labour and Welfare of Japan, the average life expectancy of Japanese people in 2016 was 80.98 years for men and 87.14 years for women [15]. This population has the highest longevity in the world. The average life expectancy of Japanese patients with diabetes is also known to be shorter than that of the general population [16].

Therefore, we aimed to evaluate the effect of postprandial hyperglycemia at clinic visits on all-cause and cancer mortality independent of mean HbA1c levels in patients with type 2 diabetes in a real-world setting. Furthermore, we investigated the age at death in patients with type 2 diabetes on a hospital basis in Japan.

2. Subjects and methods

2.1. Definitions of postprandial glycemia

Blood glucose and HbA1c levels were determined irrespective of fasting or postprandial status. At each visit, patients were asked when they had started eating their last meal, and capillary blood was drawn to determine blood glucose and HbA1c levels. A medical technologist calculated the postprandial time interval and classified it in 15-minute units. Blood glucose levels at 2 h ± 30 min after breakfast were defined as 2-hour post-breakfast blood glucose (2h-PBBG). The 2h-PBBG level that was initially measured during the 1-year period from the first visit was used as baseline data. Additionally, intrapersonal mean 2h-PBBG levels during the 3-year period from the first visit were evaluated.

In most groups of patients with type 2 diabetes, postprandial glucose excursion is more marked after breakfast than after lunch or dinner [17,18]. Therefore, we concluded that determination of 2h-PBBG levels was appropriate for evaluating postprandial hyperglycemia.

2.2. Study subjects

A flow diagram of patients included in the analyses is shown in Fig. 1. This retrospective, observational cohort study included 1582 patients with type 2 diabetes who first visited our clinic from 1995 to 1998 and continued to visit our clinic for at least 1 year. The patients were followed up for survival through 2017 and then questionnaires were mailed. Patients with an alcohol intake of 20 g or more per day were defined as drinkers.

Of these 1582 patients, 926 underwent 2h-PBBG measurements at least one time during the 1-year period after the first visit. The first measurements of 2h-PBBG levels were used as baseline data. Additionally, of these 1582 patients, 1461 were followed up for 3 years or longer. Of these 1461 patients, 1088 underwent 2h-PBBG measurements at least one time during the 3-year period after the first visit. Additional analysis using these 1088 patients was performed.

The study design followed the Japanese Government's Ethical Guidelines for Medical and Health Research Involving Human Subjects in accordance with the Declaration of Helsinki. The study was approved by the Ethics Committee of the Institute for Adult Diseases, Asahi Life Foundation.

2.3. Definition of endpoints

Endpoints were death from all causes and cancer. These endpoints were determined according to a thorough review of medical records and responses of the questionnaires. Patients who were lost to follow-up were considered censored cases at the last clinic visit. In analysis of cancer death, patients who had died from all other causes, except for cancer, were regarded as censored cases at the date of death.

2.4. Clinical examination and laboratory methods

Capillary blood glucose levels were measured by the glucose-oxidase method (Fuji DRI-CHEM; Fuji Film, Tokyo, Japan). All stated blood glucose levels are plasma equivalents. HbA1c levels were measured with a diabetes analyzer (Tosoh Bioscience, Tokyo, Japan) using a high-performance liquid chromatography method that was standardized by the Japan Diabetes Society. HbA1c values before January 2007 were converted to the Japan Diabetes Society standard for HbA1c using linear regression equations. In June 2012, all earlier HbA1c (%) values were converted to National Glycohemoglobin Standardization Program values (%) [19]. Blood pressure (BP) was generally measured once at each visit in the sitting position

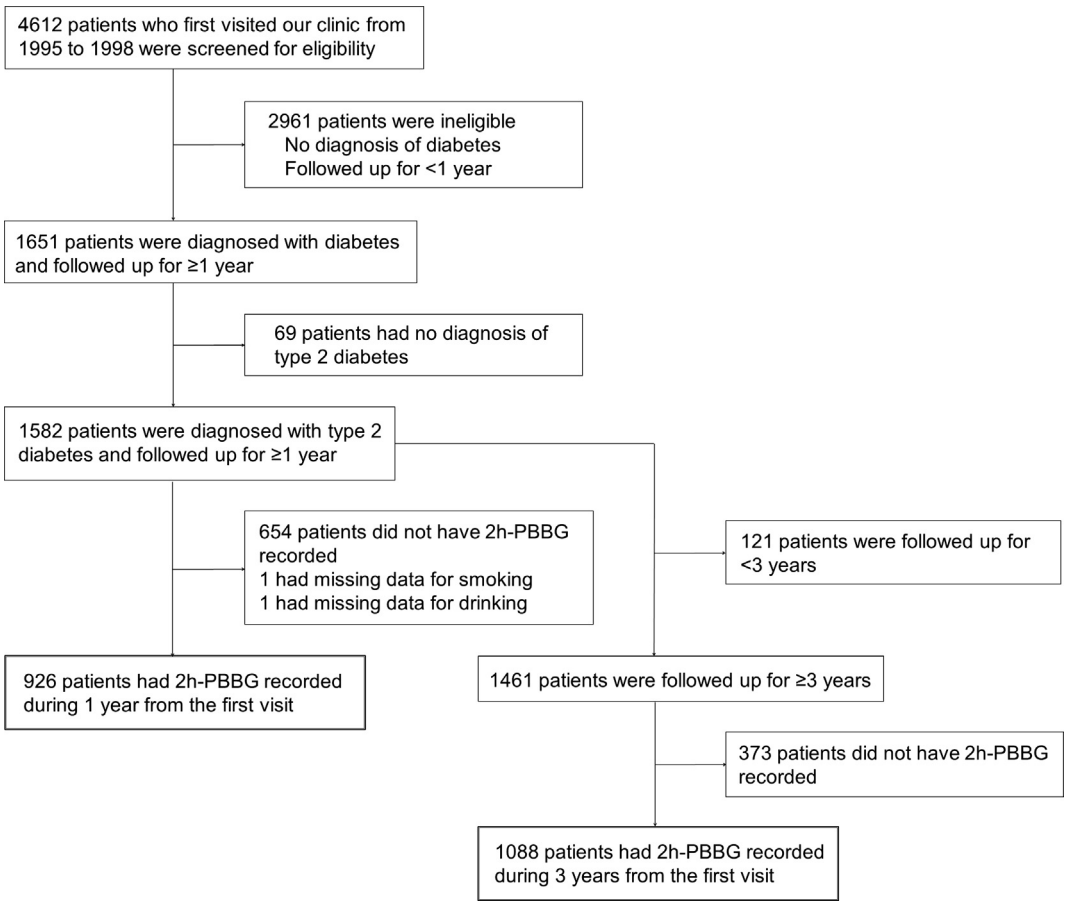

Fig. 1 – Flow diagram showing the number of patients included in the analyses.

by a trained medical technologist using an electronic sphygmomanometer (OMRON, Kyoto, Japan). Body weight was also determined at each visit.

For these clinical examination data, the values that were measured at the same time as the first measurements of 2h-PBBG levels or those immediately measured were used as baseline data. Additionally, the mean values during the initial 3 years were used.

2.5. *Statistical analysis*

Data are expressed as mean ± SD for continuous variables or as number and percentage for categorical variables. The distribution of the follow-up periods was skewed, and thus it is expressed as the median and interquartile range (IQR).

Baseline characteristics of the study participants who were analyzed and those who were excluded in the present study and those who completed and did not complete follow-up were compared. These comparisons were performed using the Student's *t*-test and Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. Differences between survivors and nonsurvivors who died from all causes or cancer were analyzed using the Student's *t*-test and Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables.

Hazard ratios (HRs) for all-cause and cancer mortality associated with 2h-PBBG levels were calculated using multivariate Cox proportional hazard models. Covariates included HbA1c levels, body mass index (BMI), systolic BP (SBP), age, sex, duration of diabetes, current smoking, and current drinking.

Intrapersonal mean 2h-PBBG levels during the 3-year period from the first visit were also analyzed. In this additional analysis, the baseline was set at 3 years after the first visit. Intrapersonal mean HbA1c levels, BMI, and SBP during the initial 3 years, age, sex, duration of diabetes, ever smoking, and ever drinking were used as covariates. When data at the 3-year visit were missing, the latest data before the 3-year visit were applied.

SAS software (version 9.4; SAS Institute, Cary, NC, USA) was used for all analyses and $p < 0.05$ in two-tailed tests was regarded as significant.

3. Results

3.1. *Outcome of the total patients*

During the follow-up of 1582 patients, 233 (186 men and 47 women) died. The mean ± SD age at death was 76.6 ± 10.3 years (75.6 ± 10.5 years in men and 80.8 ± 8.5 years in women). The median (IQR) follow-up period was 19.4 years (10.2–21.1). The overall follow-up rate was 66.8% (1056/1582). The cause of death was cancer in 79 patients, CVD in 65, infection in 24, renal failure in 11, respiratory disease in eight,

digestive disease in five, diabetes in two, other causes in 25 (senility, drowning, fall, cervical spine injury due to a fall, burn, heat stroke, asphyxia, multiple organ failure, amyotrophic lateral sclerosis, and subdural hematomas due to a fall and a traffic accident), and unknown in 14. The site of cancer was the lung in 19 patients, pancreas in 14, colon in nine, liver in six, stomach in six, prostate in six, blood in five, esophagus in three, bile duct in three, and others in eight (one case each in the adrenal gland, bladder, brain, breast, hypopharynx, ileocecal, kidney, and uterus).

3.2. Characteristics at the first visit of patients who were analyzed and those who were excluded

Table 1 shows the characteristics at the first visit of patients who were analyzed and those who were excluded in the present study. The excluded patients had significantly lower HbA1c levels ($p = 0.012$) and higher SBP ($p = 0.031$), and there was a higher proportion of current drinkers ($p = 0.038$) compared with analyzed subjects.

3.3. Levels of 2h-PBBG and outcome

Of the 926 patients, 139 died. The follow-up rate was 68.5% (634/926). Among the baseline characteristics, sex was significantly different between patients who completed (634 patients) and those who did not complete (292 patients) follow-up (70.4% completed in men, 60.6% completed in women, $p = 0.011$). The proportion of current drinkers was significantly higher in patients who completed (64.1%) than in those who did not complete (54.1%) follow-up ($p = 0.004$). The median (IQR) of the follow-up period and 2h-PBBG levels was 19.4 years (10.5–21.1) and 9.4 mmol/L (7.3–12.7), respectively.

The cause of death was cancer in 46 patients, CVD in 43, infection in 15, respiratory disease in six, renal failure in six, digestive disease in two, diabetes in one, other causes in 16 (senility, drowning, fall, burn, heat stroke, multiple organ failure, amyotrophic lateral sclerosis, and subdural hematoma due to a fall), and unknown in four. The site of cancer was the lung in nine patients, pancreas in nine, colon in six, liver in four, bile duct in three, prostate in three, stomach in three, esophagus in two, blood in two, and others in five (one case each in the adrenal gland, bladder, brain, breast, and kidney).

3.4. Baseline characteristics of survivors and nonsurvivors who died from all causes or cancer

Table 2 shows the baseline clinical characteristics of the survivors and nonsurvivors who died from all causes or cancer. Nonsurvivors who died from all causes were significantly older ($p < 0.0001$), had a longer duration of diabetes ($p = 0.0003$), had higher 2h-PBBG levels ($p = 0.027$), and had a lower proportion of current drinkers ($p = 0.044$) compared with survivors. Nonsurvivors who died from cancer were significantly older ($p < 0.0001$) and had a higher proportion of current smokers ($p = 0.015$) compared with survivors.

3.5. Postprandial glycemia and mortality from all causes and cancer

Table 3 shows the HRs for all-cause mortality and cancer mortality associated with initial 2h-PBBG levels that were calculated using a multivariate Cox proportional hazard model. For all-cause mortality, 2h-PBBG levels, age, duration of diabetes, and current smoking were significant predictors. For cancer mortality, 2h-PBBG levels, age, and current smoking were significant predictors. Levels of 2h-PBBG and current smoking were stronger predictors of cancer mortality than of all-cause mortality.

Additional analysis using intrapersonal mean 2h-PBBG levels during the initial 3 years was also performed in the same manner (Supplementary Tables 1–3). Of the 1088 patients, 169 died. The cause of death was cancer in 57 patients. The follow-up rate was 73.6% (801/1088). The median (IQR) of the follow-up period, mean 2h-PBBG levels, and the number of 2h-PBBG measurements were 16.7 years (10.9–18.2), 9.4 mmol/L (7.6–11.6), and three times (2–7), respectively. Nonsurvivors who died from all causes were significantly older ($p < 0.0001$), had a longer duration of diabetes ($p = 0.0003$), had higher mean 2h-PBBG levels ($p = 0.005$), had

Table 1 – Characteristics at the first visit of participants who were analyzed and those who were excluded in the present study.

	Total	Analyzed	Excluded
n	1582	926	656
Men (%)	1281 (81.0)	746 (80.6)	535 (81.6)
Age (years)	55.1 ± 10.0	55.5 ± 10.2	54.7 ± 9.8
Duration of diabetes (years)	6.0 ± 7.0	6.0 ± 7.1	6.1 ± 6.8
HbA1c (%) (mmol/mol)	8.1 ± 1.6 (65 ± 18)	8.2 ± 1.7 (66 ± 19)	8.0 ± 1.5 (64 ± 16)*
BMI (kg/m^2)	23.5 ± 3.5	23.4 ± 3.5	23.7 ± 3.5
SBP (mmHg)	131.7 ± 20.2	130.8 ± 19.5	133.0 ± 21.0*
DBP (mmHg)	76.7 ± 19.1	76.3 ± 22.6	77.2 ± 12.5
Current smoker	650 (41.2)	390 (42.1)	260 (39.9)
Current drinker	991 (63.0)	564 (60.9)	427 (66.1)*

Values are n (%) or mean ± SD.

BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; SBP, systolic blood pressure.

* $p < 0.05$ vs. analyzed.

Table 2 – Baseline clinical characteristics of survivors and nonsurvivors who died from all causes or cancer.

	All	Survivors	Nonsurvivors who died from all causes	p value*	Nonsurvivors who died from cancer	p value†
n	926	787	139	–	46	–
Men (%)	746 (80.6)	637 (80.9)	109 (78.4)	0.49	38 (82.6)	0.78
Age (years)	55.5 ± 10.2	53.9 ± 9.6	64.0 ± 9.2	<0.0001	60.7 ± 6.7	<0.0001
Duration of diabetes (years)	6.0 ± 7.1	5.4 ± 6.4	9.0 ± 9.9	0.0003	7.8 ± 8.9	0.072
2h-PBBG (mmol/L)	10.6 ± 4.4	10.5 ± 4.3	11.4 ± 4.8	0.027	11.9 ± 5.6	0.097
HbA1c (%) (mmol/mol)	7.3 ± 1.4 (57 ± 15)	7.3 ± 1.4 (57 ± 15)	7.5 ± 1.4 (58 ± 15)	0.18	7.4 ± 1.3 (58 ± 15)	0.67
BMI (kg/m^2)	23.0 ± 3.3	23.1 ± 3.4	22.6 ± 2.9	0.069	22.7 ± 3.1	0.43
SBP (mmHg)	127.5 ± 19.0	127.0 ± 18.5	130.6 ± 21.6	0.068	128.7 ± 21.0	0.55
DBP (mmHg)	73.2 ± 11.2	73.2 ± 11.2	73.3 ± 11.7	0.92	73.9 ± 11.3	0.67
Current smoker	390 (42.1)	335 (42.6)	55 (39.6)	0.51	28 (60.9)	0.015
Current drinker	564 (60.9)	490 (62.3)	74 (53.2)	0.044	32 (69.6)	0.32

Values are n (%) or mean ± SD.
2h-PBBG, 2-h post-breakfast blood glucose; BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; SBP, systolic blood pressure.
* Survivors vs. nonsurvivors who died from all causes.
† Survivors vs. nonsurvivors who died from cancer.

higher mean HbA1c levels (p = 0.022), and had higher mean SBP (p = 0.007) compared with survivors. Nonsurvivors who died from cancer were significantly older (p < 0.0001), had a longer duration of diabetes (p = 0.018), had higher mean 2h-PBBG levels (p = 0.020), and had a higher proportion of ever smokers (p = 0.029) compared with survivors (Supplementary Table 2). For all-cause mortality, mean 2h-PBBG levels (HR [95% confidence interval]: 1.06 [1.01–1.12], p = 0.018) (1 mmol/L increase) and age (1.13 [1.11–1.15], p < 0.0001) (1-year increase) were significant predictors. Mean HbA1c levels were borderline significant. For cancer mortality, mean 2h-PBBG levels (1.10 [1.02–1.19], p = 0.013), age (1.10 [1.06–1.14], p < 0.0001), and ever smoking (2.92 [1.18–7.26], p = 0.021) were significant predictors (Supplementary Table 3).

4. Discussion

This study showed that postprandial glycemia, which was represented by 2h-PBBG levels at a clinic visit, was associated with all-cause and cancer mortality in patients with type 2 diabetes independent of HbA1c levels in real-life conditions. Levels of 2h-PBBG that were initially measured during the 1-year period from the first visit and intrapersonal mean 2h-PBBG levels that were measured during the 3-year period from the first visit were significant predictors of all-cause and cancer deaths. These findings appear to reflect associations between mortality from all causes and cancer and initial postprandial hyperglycemia, as well as relatively early postprandial hyperglycemia including an early therapeutic effect.

Support for our findings on all-cause mortality is provided by data of the Diabetes Intervention Study [20] and the San Luigi Gonzaga Diabetes Study [21]. In the Diabetes Intervention Study, postprandial blood glucose was determined 1 h after a normal breakfast at a clinic visit, but HbA1c levels were not examined. The San Luigi Gonzaga Diabetes Study showed that 2-h blood glucose levels after lunch as measured by monitoring in the clinic and home self-monitoring predicted all-cause mortality. However, cancer mortality was not examined in these previous studies. In Japanese patients with diabetes, the most frequent cause of death is cancer, followed by infections and CVD [22,23], which differs from Western countries. To the best of our knowledge, this is the first study to indicate an association between postprandial hyperglycemia at visits to the clinic and cancer mortality in patients with type 2 diabetes independent of HbA1c levels in a real-life condition.

In patients with type 2 diabetes who were at a relatively early stage and well controlled, the insulin secretory response was sluggish for the first 2 h after ingestion of a meal [24]. This led to postprandial hyperglycemia, and resulted in hyperinsulinemia from 3 h onward. Excessive insulin action associated with insulin resistance is thought to contribute to the onset of cancer [25]. This possibility might apply to our study subjects. Therefore, concurrent endogenous hyperinsulinemia with insulin resistance and oxidative stress might contribute to the association between postprandial hyperglycemia and cancer.

We previously reported that variability of HbA1c levels could be a predictor of all-cause mortality, especially non-cancer mortality including CVD, but not cancer mortality, in

Table 3 – Multivariate Cox proportional hazard models for all-cause and cancer mortality related to initial 2-h post-breakfast blood glucose levels.

	All-cause mortality (event/patients 139/926)		Cancer mortality (event/patients 46/922[a])	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
2h-PBBG (1 mmol/L)	1.06 (1.01–1.12)	0.019	1.13 (1.03–1.24)	0.008
HbA1c (%)	0.96 (0.80–1.14)	0.62	0.76 (0.56–1.05)	0.10
Age (1 year)	1.14 (1.12–1.17)	<0.0001	1.11 (1.07–1.16)	<0.0001
Women/men	0.83 (0.52–1.35)	0.46	1.65 (0.65–4.22)	0.29
Diabetes duration (1 year)	1.02 (1.00–1.04)	0.038	1.02 (0.98–1.06)	0.39
BMI (kg/m^2)	0.99 (0.93–1.05)	0.68	1.01 (0.91–1.12)	0.89
SBP (10 mmHg)	1.04 (0.96–1.13)	0.36	0.99 (0.84–1.16)	0.87
Current smoker	1.57 (1.06–2.32)	0.024	3.54 (1.75–7.17)	0.0004
Current drinker	0.86 (0.58–1.25)	0.42	1.54 (0.75–3.16)	0.24

2h-PBBG, 2-h post-breakfast blood glucose; BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HR, hazard ratio; SBP, systolic blood pressure.

[a] Excluded those who had an unknown cause of death.

patients with type 2 diabetes independent of mean HbA1c levels [26]. Therefore, cancer mortality might be affected more by short-term glucose excursions than long-term glycemic variability, whereas all-cause mortality appears to be affected by both of these factors. This issue remains to be clarified in the future.

The average age at death of our study subjects with type 2 diabetes was 75.6 years in men and 80.8 years in women during 1996 to 2017. A previous report on Japanese patients with diabetes that was based on the results of a survey of hospital records of 45,708 cases during 2001–2010 showed that the average age at death was 71.4 years in men and 75.1 years in women [22]. Another similar survey of 18,385 Japanese patients with diabetes during 1991–2000 showed that the average age at death was 68.0 years in men and 71.6 years in women [23]. Although our results might have been overestimated because of patients lost to follow-up, the average age at death of patients with diabetes appeared to have increased with time on a hospital basis. The average life expectancy of Japanese people at 55 years in 1995 was 24.41 years for men and 29.82 years for women [27]. The NIPPON DATA 80, which was based on census tracts throughout Japan, reported that the average life expectancy of 40-year-old men and women with diabetes in 1980 was 32.3 and 40.9 years, and was 8.8 and 6.6 years shorter than that in those without diabetes, respectively [16]. The mean age of our study subjects is similar to that of participants in the NIPPON DATA 80. Differences in life expectancy between patients with diabetes and the general Japanese population might be gradually becoming smaller according to progression of management and treatment for diabetes.

The strengths of this study include the use of postprandial glycemia, as measured by monitoring in the clinic in a real-world setting, and a long-term follow-up period. Additionally, 2h-PBBG levels were evaluated in two different ways, which strengthen the results of the present study. However, there are several possible limitations of our study. First, this was a historical cohort study. Any direct causality was not determined. Potential information bias includes changes in the sample examination methods and self-reported postprandial time intervals. However, data that were generated by different measurement methods were converted using linear regression equations, which were derived from duplicate assays. The times when patients began to eat their last meal were carefully confirmed by a medical technologist and the postprandial time interval was calculated. Second, the relatively low follow-up rate for survival may have led to bias, which could be a limitation of this study. Significant differences in baseline characteristics between patients who completed and those who did not complete follow-up were found for sex and current drinking. The use of Cox regression analysis was considered to be statistically appropriate. However, the high proportion of women who did not complete follow-up may have affected the average age at death in women. Third, the number of events was small and included events that were obtained from responses of the questionnaire. In detail, 121 (51.9%) events were determined according to a thorough review of medical records, and 112 (48.1%) events were confirmed from responses of the questionnaire. Further studies with a larger sample size and a higher follow-up rate are required to confirm our findings. Fourth, the average age at death of our subjects with type 2 diabetes was considered to be lower than that of the general Japanese population, but was obviously higher than that of previous surveys of patients with diabetes [22,23,27]. Therefore, our study subjects might have been a well-managed group. Finally, the study subjects were from a single hospital in Japan and included more men than women. Therefore, generalizability of our results to other populations is limited.

In conclusion, postprandial hyperglycemia expressed as 2h-PBBG levels at clinic visits may be associated with all-cause and cancer mortality in patients with type 2 diabetes independent of HbA1c levels in a real-world setting. The average age at death of patients with type 2 diabetes might be approaching that of people without diabetes in the Japanese population. Further studies are warranted to confirm our findings.

Author contributions

T.T. contributed to the study concept and design, collection and recording of data, data analyses and interpretation, and

writing of the manuscript. K.T. contributed to collection and recording of data. N.S. contributed to collection and recording of data and discussion of the implications of this work. M.S. and H.Y. contributed to discussion of the implications of this work. TT is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

The authors thank all of the study participants for their cooperation in collecting information and completing the questionnaires. The authors thank Ms. Kumiko Kimura and the General Affairs Department staffs at the Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan, for their assistance with collection of research data and preparing and mailing of the questionnaires. We thank Ellen Knapp, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Prior Presentation. Part of this study was presented at the 54th annual meeting of the European Association for the Study of Diabetes, Berlin, Germany, 1–5 October, 2018.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.006.

REFERENCES

[1] Jalving M, Gietema JA, Lefrandt JD, de Jong S, Reyners AK, Gans RO, et al. Metformin: taking away the candy for cancer? Eur J Cancer 2010;46:2369–80.
[2] Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. Diab Care 2010;33:1674–85.
[3] de Beer JC, Liebenberg L. Does cancer risk increase with HbA1c, independent of diabetes? Br J Cancer 2014;110:2361–8.
[4] Travier N, Jeffreys M, Brewer N, Wright CS, Cunningham CW, Hornell J, et al. Association between glycosylated hemoglobin and cancer risk: a New Zealand linkage study. Ann Oncol 2007;18:1414–9.
[5] The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364: 829–41.
[6] Hirakawa Y, Ninomiya T, Mukai N, Doi Y, Hata J, Fukuhara M, et al. Association between glucose tolerance level and cancer death in a general Japanese population: the Hisayama Study. Am J Epidemiol 2012;176:856–64.
[7] Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 2006;295:1681–7.
[8] Sala LL, Cattaneo M, De Nigris V, Pujadas G, Testa R, Bonfigli AR, et al. Oscillating glucose induces microRNA-185 and impairs an efficient antioxidant response in human endothelial cells. Cardiovasc Diabetol 2016;15:71.
[9] Akatsuka S, Toyokuni S. Genome-wide assessment of oxidatively generated DNA damage. Free Radic Res 2012;46:523–30.
[10] Bondia-Pons I, Ryan L, Martinez JA. Oxidative stress and inflammation interactions in human obesity. J Physiol Biochem 2012;68:701–11.
[11] Raz I, Wilson PWF, Strojek K, Kowalska I, Bozikov V, Gitt AK, et al. Effects of prandial versus fasting glycemia on cardiovascular outcomes in type 2 diabetes: the HEART2D trial. Diab Care 2009;32:381–6.
[12] Raz I, Ceriello A, Wilson PW, Battioui C, Su EW, Kerr L, et al. Post hoc subgroup analysis of the HEART2D trial demonstrates lower cardiovascular risk in older patients targeting postprandial versus fasting/premeal glycemia. Diab Care 2011;34:1511–3.
[13] Mannucci E, Monami M, Lamanna C, Adalsteinsson JE. Postprandial glucose and diabetic complications: systematic review of observational studies. Acta Diabetol 2012;49:307–14.
[14] Takao T, Suka M, Yanagisawa H, Iwamoto Y. Impact of postprandial hyperglycemia at clinic visits on the incidence of cardiovascular events and all-cause mortality in patients with type 2 diabetes. J Diab Investig 2017;8:600–8.
[15] The Ministry of Health, Labour, and Welfare. Abridged Life Tables for Japan 2016. Available at <https://www.mhlw.go.jp/toukei/saikin/hw/life/life16/dl/life16-06.pdf> and <https://www.mhlw.go.jp/toukei/saikin/hw/life/life16/dl/life16-07.pdf>.
[16] Turin TC, Murakami Y, Miura K, Rumana N, Kadota A, Ohkubo T, et al. Diabetes and life expectancy among Japanese – NIPPON DATA80. Diab Res Clin Pract 2012;96:e18–22.
[17] Peter R, Dunseath G, Luzio SD, Chudleigh R, Roy Choudhury S, Owens DR. Daytime variability of postprandial glucose tolerance and pancreatic B-cell function using 12-h profiles in persons with type 2 diabetes. Diab Med 2010;27:266–73.
[18] Monnier L, Colette C, Owens DR. Integrating glycemic variability in the glycaemic disorders of type 2 diabetes: a move towards a unified glucose tetrad concept. Diab Metab Res Rev 2009;25:393–402.
[19] Kashiwagi A, Kasuga M, Araki E, Oka Y, Hanafusa T, Ito H, et al. International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. J Diab Investig 2012;3:39–40.
[20] Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. Diabetologia 1996;39:1577–83.
[21] Cavalot F, Pagliarino A, Valle M, Di Martino L, Bonomo K, Massucco P, et al. Postprandial blood glucose predicts cardiovascular events and all-cause mortality in type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. Diab Care 2011;34:2237–43.
[22] Nakamura J, Kamiya H, Haneda M, Inagaki N, Tanizawa Y, Araki E, et al. Causes of death in Japanese patients with diabetes based on the results of a survey of 45,708 cases during 2001–2010: report of the Committee on Causes of Death in Diabetes Mellitus. J Diab Invest 2017;8:397–410.
[23] Hotta N, Nakamura J, Iwamoto Y, Ohno Y, Kasuga M, Kikkawa R, et al. Causes of death in Japanese diabetics: a questionnaire survey of 18,385 diabetics over a 10-year period. J Diab Invest 2010;1:66–76.

[24] Basu A, Dalla Man C, Basu R, Toffolo G, Cobelli C, Rizza RA. Effects of type 2 diabetes on insulin secretion, insulin action, glucose effectiveness, and postprandial glucose metabolism. Diab Care 2009;32:866–72.
[25] Kasuga M, Ueki K, Tajima N, Noda M, Ohashi K, Noto H, et al. Report of the JDS/JCA Joint Committee on diabetes and cancer. Diabetol Int 2013;4:81–96.
[26] Takao T, Matsuyama Y, Yanagisawa H, Kikuchi M, Kawazu S. Association between HbA1c variability and mortality in patients with type 2 diabetes. J Diab Complicat 2014;28:494–9.
[27] The Ministry of Health, Labour, and Welfare. 2–35 Complete Life Table (1891–2000). Available at <www.stat.go.jp/data/chouki/zuhyou/02-35.xls>.