Thresholds for postprandial hyperglycemia and hypertriglyceridemia associated with increased mortality risk in type 2 diabetes patients: A real-world longitudinal study

Toshiko Takao¹*, Machi Suka², Hiroyuki Yanagisawa²*, Masato Kasuga¹

¹Division of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan, ²Department of Public Health and Environmental Medicine, The Jikei University School of Medicine, Tokyo, Japan

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*Correspondence
Toshiko Takao
Tel: +81-3-3639-5501
Fax: +81-3-3639-5520
E-mail address: t-takao@asahi-life.or.jp

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ABSTRACT
Aims/Introduction: To identify thresholds for postprandial hyperglycemia and hypertriglyceridemia predictive of all-cause mortality in patients with type 2 diabetes.

Materials and Methods: A total of 1,928 patients with type 2 diabetes visited our clinic for the first time from 1995 to 1999 and were followed up for ≥1 year. During the first year, 2-h post-breakfast blood glucose (2h-BG) levels were measured in 1,122 patients (BG cohort) and postprandial serum triglyceride (ppTG) levels were measured in 1,826 patients (TG cohort). Patients were retrospectively followed until 2017 and administered questionnaires. Associations between 2h-BG and ppTG levels and mortality risk were assessed by the multivariate Cox regression analysis.

Results: Over 17,429 person-years, 162 deaths occurred in the BG cohort, and over 28,026 person-years, 253 deaths occurred in the TG cohort. Hazard ratios (HRs) with 95% confidence intervals for all-cause mortality per 1-standard deviation increases in 2h-BG and ppTG were 1.34 (1.08–1.67) and 1.24 (1.06–1.45), respectively. HRs showed increasing trends across quintiles of 2h-BG (P = 0.034) and ppTG (P = 0.007). The HR was significantly elevated (2.37, 1.26–4.47) in the fifth quintile of 2h-BG (≥13.8 mmol/L) compared with the first quintile (<7.0 mmol/L; P = 0.008). The HR was also significantly elevated (1.63, 1.03–2.60) in the fifth quintile of ppTG (≥2.30 mmol/L) compared with the first quintile (<0.91 mmol/L; P = 0.038).

Conclusions: Postprandial hyperglycemia and hypertriglyceridemia were associated with all-cause mortality in patients with type 2 diabetes. We propose thresholds of 13.8 mmol/L 2h-BG and 2.30 mmol/L ppTG to identify patients at increased risk of mortality.

INTRODUCTION
Several epidemiological studies have reported associations between postprandial, but not post-load, hyperglycemia and adverse events in diabetes patients¹–⁷. Our previous studies showed that postprandial hyperglycemia at clinic visits was associated with the incidence of diabetic retinopathy, cardiovascular disease (CVD), all-cause mortality and cancer mortality⁵–⁷. Postprandial hyperglycemia has negative impacts on surrogate measures, such as endothelial dysfunction, in diabetes patients. For many non-pregnant adults with diabetes, glycemic recommendations are a glycated hemoglobin A1c (HbA1c) level of <7% (53 mmol/mol), preprandial capillary plasma glucose levels of 4.4–7.2 mmol/L and peak postprandial capillary plasma glucose levels of 10.0 mmol/L⁸. Capillary plasma glucose levels that seem to correlate with achieving an HbA1c level of <7% have been determined as the recommended target⁸. However, the threshold for postprandial capillary plasma glucose levels that is predictive of adverse events has not been determined in diabetes patients.
Multiple epidemiological studies have evaluated associations between postprandial hypertriglyceridemia and adverse events in the general population. Various panels have proposed different cut-offs for non-fasting hypertriglyceridemia; these include 2.26 mmol/L by the American Heart Association, 2.03 mmol/L by the Athens Expert Panel, and 1.98 mmol/L by the European Atherosclerosis Society. A study of participants in the Women’s Health Study also recommended a diagnostic threshold of 1.98 mmol/L for non-fasting hypertriglyceridemia. However, no studies have assessed the relationship between postprandial hypertriglyceridemia and mortality risk in diabetes patients.

Here, we assessed the relationships between all-cause mortality and postprandial hyperglycemia and hypertriglyceridemia in patients with type 2 diabetes in a real-world setting. We estimated thresholds for postprandial glycemia and triglyceridemia that are predictive of all-cause mortality.

**METHODS**

**Definition of postprandial glycemia and triglyceridemia**

Capillary blood glucose (BG) levels were measured as previously reported. BG levels were presented as plasma equivalents. Laboratory technologists checked when the patients had eaten their last meal, and postprandial time intervals were recorded every 15 min. Postprandial glycemia was defined as 2-h post-breakfast BG (2h-BG) levels, which were measured 2 h ± 30 min after breakfast. Lipid levels were measured every few visits using serum prepared from venous blood regardless of fasting or postprandial conditions. Triglyceride (TG) levels were measured by an enzymatic method. Non-fasting serum TG levels were defined as postprandial TG (ppTG) levels. The first observations taken in the first year were taken as the baseline 2h-BG and ppTG levels.

**Study participants**

Figure 1 shows a flowchart of the study cohorts. A total of 1,928 patients with type 2 diabetes visited the clinic at the Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan, for the first time between 1995 and 1999, and were followed up for 18.7 years (10.1–20.7 years) in the BG cohort, and 18.6 years (9.2–20.7 years) in the TG cohort. The percentages of patients completing follow up were 68.4% (767/1,122) in the BG cohort, and 66.7% (1,218/1,826) in the TG cohort. Table S1 shows differences in the baseline characteristics between patients with...
and without complete follow up. In the BG cohort, the percentages of men and alcohol consumers were significantly higher in patients who completed (81.9 and 60.5%, respectively) than in those who did not complete (74.4 and 50.4%, respectively) follow up ($P = 0.004$ and $P = 0.002$, respectively). Similarly, in the TG cohort, the percentages of men and alcohol consumers were significantly higher in patients who completed (81.9 and 61.7%, respectively) than in those who did not complete (76.6 and 54.0%, respectively) follow up ($P = 0.008$ and $P = 0.001$, respectively). No significant differences were observed in any other variables (Table S1).

**Baseline findings in the BG and TG cohorts**

Table 1 summarizes the baseline characteristics of the BG and TG cohorts, as a whole, and stratified by quintiles of 2h-BG and ppTG levels (natural logarithm). Higher 2h-BG levels were associated with younger age, longer diabetes duration, higher systolic BP and diastolic BP, higher HbA1c levels, higher TC levels, lower HDL-C levels, and higher estimated glomerular filtration rate. Higher 2h-BG levels were also associated with male sex, current smoking, use of oral antidiabetic drugs and use of insulin. Higher ppTG levels were associated with higher body mass index, higher systolic BP and diastolic BP, higher HbA1c levels, higher TC levels, and lower HDL-C levels. Higher ppTG levels were also associated with male sex, current smoking, history of CVD, use of oral antidiabetic drugs, antihypertensive agents and agents for dyslipidemia (Table 1).

**Associations between 2h-BG and ppTG levels and risk of all-cause mortality**

Over 17,429 person-years, 162 deaths occurred in the BG cohort, and over 28,026 person-years, 253 deaths occurred in the TG cohort. The crude incidence ratios (per 1,000 person-years) were 9.29 (95% confidence interval [CI] 3.68–14.90) in the BG cohort, and 9.03 (95% CI 4.69–13.37) in the TG cohort.

Adjusted hazard ratios (HRs) for all-cause mortality in each quintile of 2h-BG and ppTG levels are shown in Table 2. The HRs showed increasing trends across quintiles of 2h-BG ($P$ for linear trend = 0.034) and ppTG ($P$ for linear trend = 0.007). The HR was significantly elevated (2.37, 95% CI 1.26–4.47) in the fifth quintile ($\geq 13.8$ mmol/L) of the 2h-BG levels compared with the first quintile (<7.0 mmol/L; $P = 0.008$). The HR was significantly elevated (1.63, 95% CI 1.03–2.60) in the fifth
Table 1 | Baseline characteristics of the BG and TG cohorts stratified by quintiles of 2-h post-breakfast blood glucose and postprandial serum triglyceride levels

| BG cohort | Quintiles of 2h-BG levels (mmol/L) | TG cohort | Quintiles of ppTG<sup>2</sup> levels (mmol/L) |
|-----------|-----------------------------------|-----------|---------------------------------|
|           | Q 1                               | Q 2       | Q 3                             | Q 4                     | Q 5                  | P-value |
|           | > 7.0                              | 7.0-8.7   | 8.7-10.7                        | 10.7-13.8               | ≥ 13.8               |         |
| n         | 1,122                             | 220 (196) | 224 (200)                       | 235 (201)               | 226 (201)            | 1,836   |
| Men (%)   | 892 (79.5)                        | 162 (73.6)| 175 (781)                       | 179 (792)               | 188 (883)            | 0.005   |
| Age (years) | 559 ± 101                      | 55 ± 110  | 57 ± 96                          | 53 ± 94                 | 56 ± 100             | 0.034   |
| Duration of diabetes (years) | 61 ± 70                        | 39 ± 60   | 50 ± 70                          | 60 ± 66                 | 71 ± 77              | <0.0001 |
| BMI (kg/m<sup>2</sup>) | 231 ± 33                        | 226 ± 35  | 229 ± 30                         | 233 ± 33                | 232 ± 33             | 0.006   |
| SBP (mmHg) | 1276 ± 193                      | 1222 ± 181| 1274 ± 186                       | 1290 ± 182              | 1284 ± 204           | <0.0001 |
| DBP (mmHg) | 731 ± 113                       | 704 ± 107 | 728 ± 109                        | 739 ± 106               | 735 ± 124            | 0.0003  |
| 2h-BG (mmol/L) | 106 ± 44                      | 60 ± 07   | 78 ± 05                          | 96 ± 06                 | 121 ± 09             | <0.0001 |
| ppTG<sup>2</sup> (mmol/L) | –                                | –        | –                               | –                      | –                   | –       |
| HbA1c (%) | 73 ± 14                          | 64 ± 08   | 67 ± 08                          | 71 ± 10                 | 75 ± 10              | <0.0001 |
| (mmol/mol) | (57 ± 16)                       | (47 ± 9)  | (50 ± 9)                         | (54 ± 11)               | (58 ± 11)            | (75 ± 17)|
| TC (mmol/L) | 542 ± 096                       | 533 ± 091 | 547 ± 098                        | 546 ± 103               | 530 ± 099            | 0.0496  |
| HDL-C (mmol/L) | 135 ± 037                      | 142 ± 038 | 140 ± 039                        | 138 ± 039               | 124 ± 031            | <0.0001 |
| eGFR (ml/min/1.73 m<sup>2</sup>) | 788 ± 179                      | 771 ± 178 | 750 ± 177                        | 790 ± 179               | 802 ± 156            | <0.0001 |
| Current smoker | 469 (41.8)                     | 84 (38.2) | 84 (37.5)                        | 79 (35.0)               | 108 (47.8)           | 0.0008  |
| Alcohol intake | 643 (57.3)                     | 112 (50.9)| 113 (589)                        | 131 (61.8)              | 129 (571)            | 0.19    |
| History of CVD | 7 (0.6)                        | 1.05 (5.0)| 3 (14.1)                         | 1 (0.4)                 | 1 (0.4)              | 0.057   |
| History of cancer | 13 (1.2)                      | 4 (1.8)   | 5 (2.2)                          | 1 (0.4)                 | 1 (0.4)              | 0.011   |
| Initial therapies | 456 (40.6)                   | 67 (30.5) | 75 (33.5)                        | 85 (37.6)               | 108 (47.8)           | <0.0001 |
| Oral antidiabetic | 180 (16.4)                    | 34 (15.6) | 16 (7.1)                          | 29 (12.8)               | 35 (15.9)            | 0.006   |
| Insulin | 180 (16.4)                        | 34 (15.6) | 16 (7.1)                          | 29 (12.8)               | 35 (15.9)            | 0.006   |
| Antihypertensive agents | 237 (21.1)                   | 33 (15.0) | 55 (24.6)                        | 50 (22.1)               | 43 (19.0)            | 0.011   |
| Lipid-lowering agents | 138 (12.3)                   | 29 (13.2) | 33 (14.7)                        | 27 (12.0)               | 19 (8.4)             | 0.38    |

The 2-h post-breakfast blood glucose (2h-BG) and postprandial serum triglyceride (ppTG) levels initially measured during the 1-year period starting at the first visit were used as the baseline. Clinical data measured at the same time or most immediately measured as the first measurements of 2h-BG or ppTG were used as the baseline. BG, blood glucose; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride. Values represent n (%) or means ± standard deviations. *ln-transformed.
quintile (≥2.30 mmol/L) of the ppTG levels compared with the first quintile (<0.91 mmol/L; \( P = 0.038 \); Table 2). The second to fourth quintiles of 2h-BG and ppTG levels were not significantly different compared with the first quintile. The second quintile of 2h-BG and ppTG levels had the lowest HRs, but \( P \)-values for the quadratic trend were not significant. Covariates are described in the statistical analysis section. These relationships are described in the statistical analysis section. These relationships are plotted in Figure 2.

HRs for all-cause mortality per 1-SD increases in 2h-BG and ppTG levels were 1.34 (95% CI 1.08–1.67) and 1.24 (95% CI 1.06–1.45), respectively, after adjusting for the same covariates (models 1 and 2 in Table 3). After further adjusting for users of oral antidiabetic drugs, insulin, antihypertensive agents and agents for dyslipidemia, HRs per 1-SD increases in 2h-BG and ppTG levels were 1.34 (95% CI 1.07–1.68) and 1.18 (95% CI 1.00–1.39), respectively (models 3 and 4 in Table 3). Therefore, similar results were obtained when the effects of drug administration were further adjusted. Consequently, the present results were independent of drug administration. Additionally, no interaction was observed between 2h-BG and HbA1c levels (\( P = 0.69 \)).

Kaplan–Meier curves in patients stratified using the estimated thresholds for 2h-BG and ppTG levels

The BG and TG cohorts were stratified using the estimated 2h-BG threshold of 13.8 mmol/L and the estimated ppTG threshold of 2.30 mmol/L, respectively. Kaplan–Meier curves in patients who were stratified using these 2h-BG and ppTG thresholds showed increasing risk separation from approximately 2 and 5 years, respectively (Figure 3).

**DISCUSSION**

Here, we showed that postprandial hyperglycemia and hypertriglyceridemia at clinic visits were associated with an increased risk of all-cause mortality in real-world patients with type 2 diabetes. We propose approximate thresholds of 13.8 mmol/L for 2h-BG and 2.30 mmol/L for ppTG to identify patients at high risk of mortality.

Our previous study showed that postprandial hyperglycemia at clinic visits was associated with all-cause mortality in patients with type 2 diabetes. However, there is no evidence for a threshold of postprandial glycemia predictive of mortality in patients with type 2 diabetes. In this real-world study, an estimated threshold for postprandial glycemia was identified.

Time in range (3.9–10.0 mmol/L), that is a new metric derived from continuous glucose monitoring, is associated with the risk of microvascular complications. A strong correlation between time in range and HbA1c levels was observed, with a time in range of 70% equating to a HbA1c level of 7%. Additionally, as targets for achieving control, time above range of >10.0 mmol/L was proposed for <25% of readings, and time above range of >13.9 mmol/L was proposed for <5% of readings. In the present study, the threshold for 2h-BG predictive of mortality may correspond to a target of time above range for <5% of readings.

In a prospective study from the Danish general population, non-fasting hypertriglyceridemia was associated with the incidence of myocardial infarction, ischemic heart disease and all-cause mortality. Later, after 31 years of follow up, the same study reported that non-fasting hypertriglyceridemia was
showed that non-fasting hypertriglyceridemia was associated with the incidence of CVD independent of classical risk factors, but fasting hypertriglyceridemia showed little independent association. In a study of residents in four Japanese communities, non-fasting triglyceride levels predicted the incidence of ischemic CVD. The results of these studies support our results, but no previous study assessed the mortality risk related to non-fasting hypertriglyceridemia in diabetes patients. To our knowledge, ours is the first study to show that non-fasting hypertriglyceridemia was associated with all-cause mortality in patients with type 2 diabetes.

Postprandial hypertriglyceridemia is associated with CVD risk, and is relevant to an increase in chylomicron remnant lipoproteins derived from the intestine. In diabetes patients, remnant lipoprotein cholesterol levels persist high all day long, with the exception of a few hours before breakfast. Insulin resistance accelerates the postprandial accumulation of remnant lipoproteins. Therefore, the characterization of postprandial lipid profiles is important for patients with diabetes. Various cut-offs for postprandial hypertriglyceridemia for prediction of adverse events were proposed in general populations. However, there is no evidence for a threshold of postprandial hypertriglyceridemia predictive of mortality in diabetes patients. In this real-world study, we identified an estimated threshold for postprandial triglyceride predictive of mortality in patients with type 2 diabetes. Further research is required to validate our results.

The present study’s strengths included the analysis of postprandial glycemia and triglyceride levels, as measured by monitoring in the outpatient clinic in a real-life condition, and a long-term follow up. Several potential limitations deserve consideration. First, this was a historical cohort study. Changes in measurement methods and self-reported postprandial time intervals may have led to information bias. However, using linear regression equations from duplicate assays, data obtained using different measurement methods could be converted. The time when patients started eating their last meal was thoroughly assessed by a laboratory technician and postprandial time intervals were determined. Data were excluded if snacks between meals were

Table 3 | Multivariate Cox proportional hazards models of the associations between all-cause mortality and 2-h post-breakfast blood glucose and postprandial serum triglyceride levels

| BG cohort (events/patients 162/1,122) | TG cohort (events/patients 253/1,826) |
|--------------------------------------|--------------------------------------|
| **Model 1**                          | **Model 2**                           |
| 2h-BG (1 SD; mmol/L)                 | ppTG† (1 SD; mmol/L)                  |
| HR (95% CI)                          | HR (95% CI)                           |
| 1.34 (1.08–1.67)                     | 1.24 (1.06–1.45)                     |
| *P*-value                            | *P*-value                            |
| 0.009                                | 0.008                                |
| **Model 3**                          | **Model 4**                           |
| 2h-BG (1 SD; mmol/L)                 | ppTG† (1 SD; mmol/L)                  |
| HR (95% CI)                          | HR (95% CI)                           |
| 1.34 (1.07–1.68)                     | 1.18 (1.00–1.39)                     |
| *P*-value                            | *P*-value                            |
| 0.010                                | 0.045                                |

Models 1 and 2 were adjusted for age, sex, diabetes duration, body mass index, systolic blood pressure, HbA1c levels, total cholesterol levels, high-density lipoprotein cholesterol levels, current smoking, alcohol intake, history of cardiovascular disease and history of cancer. Models 3 and 4 were adjusted for the use of oral antidiabetic drugs, insulin, antihypertensive agents and agents for dyslipidemia in addition to the covariates included in models 1 and 2. †Ln-transformed. 2h-BG, 2-h post-breakfast blood glucose; ppTG, postprandial serum triglyceride; SD, standard deviation.
consumed and if meals were consumed following hypoglycemia. Second, bias may have occurred because of relatively high losses to follow up. Significant differences in baseline characteristics between patients with and without complete follow up were identified for sex and alcohol consumption (Table S1). Third, almost half of the events were found in the questionnaire replies. In the BG and TG cohorts, a thorough review of medical charts, recorded by the attending physician, documented 82 (51%) and 124 (49%) deaths, respectively, and replies to questionnaires by family members confirmed 80 (49%) and 129 (51%) deaths, respectively. Fourth, 2h-BG and ppTG levels were measured after an ordinary meal, without standardization of dietary intake. However, the present study aimed to evaluate the effects of postprandial hyperglycemia and hypertriglyceridemia at clinic visits on mortality using real-world data. Therefore, standardization of dietary intake was not considered. Finally, the study participants were enrolled in a single Japanese clinic. Therefore, generalizability to other ethnicities may be limited.

In conclusion, postprandial hyperglycemia and hypertriglyceridemia at clinic visits were associated with an increased risk of all-cause mortality in real-world patients with type 2 diabetes. We propose 2h-BG levels of 13.8 mmol/L and ppTG levels of 2.30 mmol/L as estimated thresholds to identify patients at increased risk of all-cause mortality.

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DISCLOSURE
The authors declare no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Comparison of baseline characteristics between patients who did and did not complete follow-up in the BG and TG cohorts.