Association of insulin treatment with gastric residue during an esophagogastroduodenoscopy

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ABSTRACT
The purpose of this study was to investigate the association of glycemic control and diabetes treatment to gastric residue observed during an esophagogastroduodenoscopy. Among 6,592 individuals who had esophagogastroduodenoscopy at our clinic between 2003 and 2019, we retrospectively and longitudinally identified those who had gastric residue during an esophagogastroduodenoscopy. Other data collected were age, sex, diagnosis of diabetes, glycated hemoglobin and diabetes medication. Cox proportional hazards models were used to assess the association of these data with the occurrence of gastric residue. To the best of our knowledge, this is the first retrospective cohort study finding that undergoing insulin treatment is a risk factor for gastric residue independent of age, sex and diabetes or glycated hemoglobin.

INTRODUCTION
Gastrointestinal diabetic autonomic neuropathy induces gastrointestinal motility disorder, such as gastroparesis and diabetic enteropathies1. Multiple studies have previously reported that diabetes is one of the risk factors for inadequate bowel preparation for a colonoscopy2-5. In contrast, there is no obvious report on the association between diabetes and gastric residue during an esophagogastroduodenoscopy. The purpose of the present retrospective cohort study was to investigate whether diabetes, glycemic control or insulin treatment were the risk factors for gastric residue during an esophagogastroduodenoscopy.

MATERIAL AND METHODS
The present study was a retrospective cohort study. The protocol was approved by the Committee of Ethics in the Institute of Medical Science, Asahi Life Foundation (approval number 11609). Informed consent was obtained in the form of opt-out on our website. Investigations were carried out in accordance with the principals of the Declaration of Helsinki.

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The study population was individuals who had an esophagogastroduodenoscopy at our clinic between January 2003 and December 2019. Among 11,416 individuals, we excluded 136 individuals with a history of esophageal or gastric operation, one individual who had gastrointestinal obstruction by small intestinal cancer and 3,554 individuals who did not test glycated hemoglobin (HbA1c) at our clinic within 6 months before the first esophagogastroduodenoscopy. We also excluded 1,133 individuals without abnormal findings at the first esophagogastroduodenoscopy to focus on individuals who needed to undergo esophagogastroduodenoscopy regularly. Finally, the study comprised of 6,592 participants.

All participants started fasting before 21.00 hours on the previous day of the esophagogastroduodenoscopy, and consumed nothing except for water afterwards. All esophagogastroduodenoscopies were carried out between 09.00 and 11.30 hours. Therefore, the duration of fasting of all participants was ≥12 h, which should be enough to empty the stomach6. All esophagogastroduodenoscopy findings were reported by trained gastroenterologists who carried out the esophagogastroduodenoscopy. We defined the presence of gastric residue as having any solids in the stomach during an esophagogastroduodenoscopy.
We defined having diabetes as either taking diabetes medical treatment, fasting blood glucose level ≥126 mg/dL, casual blood glucose level ≥200 mg/dL, HbA1c ≥6.5% or self-report in a questionnaire.

HbA1c levels measured by the certified National Glycohemoglobin Standardization Program (NGSP) were used for the analysis. HbA1c levels measured by the Japan Diabetes Society (JDS) standard values were converted to HbA1c (NGSP) using the following formula: HbA1c (NGSP) (%) = 1.02 × HbA1c (JDS) + 0.25. We used the latest HbA1c and the diabetes prescription within 6 months before the first esophagogastroduodenoscopy for the baseline characteristics of this analysis. Other data collected were age, sex and diabetes medication at the first esophagogastroduodenoscopy. Data of the duration of diabetes were not available for most of the diabetes patients.

The outcome was the presence of gastric residue during esophagogastroduodenoscopy. Follow-up time was defined as the time from the first date of an esophagogastroduodenoscopy between January 2003 and December 2019 until the date of the outcome or the last date of an esophagogastroduodenoscopy during the duration of this study, whichever came first. Participants who did not have gastric residue were considered censored cases. We regarded observational periods as 0.5 days when participants had gastric residue at the first esophagogastroduodenoscopy. To assess the linearity of the association between HbA1c and gastric residue, HbA1c was checked by categorizing the continuous variable into quartiles and visually assessing the scatter plot of each variable’s coefficient in the Cox proportional hazard models against the median value of each class of dichotomous variables. This method confirmed a non-linear association between gastric residue and HbA1c. Therefore, we combined the groups of categorized HbA1c with close regression coefficients to obtain two groups: (i) the three lowest quartiles, HbA1c <7.5%; and (ii) the highest quartile, HbA1c ≥7.5%. Similarly, in the subgroup analysis on diabetes patients, we divided HbA1c into two groups: (1) HbA1c <8.2%; and (ii) HbA1c ≥8.2%. These categorized HbA1c were treated as multiple dichotomous variables in the Cox proportional hazards analysis. Multicollinearity of the model was assessed by using the variance inflation factor and the variance inflation factor was confirmed to be smaller <2.5. The threshold of statistical significance was two-tailed \( P < 0.05 \).

Statistical analyses were carried out using JMP version 16.0.0 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The baseline characteristics of 6,564 without gastric residue and of 28 with gastric residue are shown in Table 1. Higher HbA1c and insulin treatment significantly increased the risk of the presence of gastric residue in univariate analysis.

In multivariate Cox proportional hazards models, adjusted for age and sex, having diabetes was not a significant factor, but HbA1c ≥7.5% significantly increased the risk of gastric residue (Table 2: model 1 and 2). Next, we assessed the association of undergoing insulin treatment with gastric residue. Insulin treatment was an independent risk factor for gastric residue, adjusted for age, sex and diabetes (Table 2: model 3) or HbA1c (Table 2: model 4).

Furthermore, we carried out subgroup analysis on diabetes patients. The baseline characteristics of 3,799 diabetes patients are shown in Table 3. Although HbA1c did not show a significant association (Table 4: model 1), insulin treatment was significantly associated with gastric residue in multivariate analysis, adjusted for age, sex and HbA1c (Table 4: model 2).

DISCUSSION

The present retrospective cohort study showed that insulin treatment was a risk factor for gastric residue during an esophagogastroduodenoscopy.

Although there is no obvious report on the association between diabetes and gastric residue during an esophagogastroduodenoscopy to our knowledge, some previous studies reported that diabetes was a risk factor for inadequate bowel preparation for a colonoscopy. As for glycemic control and insulin treatment in diabetes patients, some studies showed that there is no significant association between quality of bowel preparation and HbA1c, and between the quality of bowel preparation and undergoing insulin treatment. However, in the present study, insulin treatment was a significant risk factor for gastric residue during an esophagogastroduodenoscopy adjusted for diabetes or HbA1c.

Patients undergoing insulin treatment often have a long diabetes history. A multicentered observational study of type 2 diabetes in Japan showed that the mean diabetes duration of patients with insulin therapy was significantly longer than patients with oral hypoglycemic agents (10.3 vs 7.2 years). In the present study, we were able to acquire the duration of diabetes of those with gastric residue and the median was 16 years (interquartile range 9–21 years). Therefore, if we assume that undergoing insulin therapy is a surrogate marker of diabetes duration, the present results might suggest that the duration of diabetes is a risk factor for the presence of gastric residue. It might be plausible, because it is reported that long duration of diabetes is a risk factor of diabetic neuropathy and gastroparesis is one of the phenotypes of diabetic autonomic neuropathy. Further investigation is necessary to clarify the association between diabetes duration and gastric residue.

Several limitations of the present study should be acknowledged. First, we were unable to obtain the information of diabetes duration from most of the participants. Second, there remains the possibility that prescription from other hospitals affected gastrointestinal motility. Third, gastric residue might be underestimated, because gastroenterologists might not list it in the case of a small amount of gastric residue. Finally, we were unable to confirm the association of glucagon-like peptide-1 analog treatment with gastric residue because there was only one subject with gastric residue taking the treatment. Further study is needed to elucidate this relationship.
In summary, the present retrospective cohort study shows for the first time that undergoing insulin treatment is a risk factor for gastric residue during an esophagogastroduodenoscopy independent of age, sex and diabetes or HbA1c.

Table 1 | Characteristics of study participants according to the presence of gastric residue

| Variable            | Total  n = 6,592 | No gastric residue  n = 6,564 | Gastric residue (+)  n = 28 | HR       | 95% CI         | P-value |
|---------------------|-----------------|-----------------------------|-----------------------------|----------|----------------|---------|
| Age (years)         |                 |                             |                             |          |                |         |
| 63 (55–70)          | 63 (55–70)      | 63 (56.5–68.8)              | 0.99                        | 0.96–1.03 | 0.781          |         |
| Sex (male)          | 4,669 (70.8)    | 4,647 (70.8)                | 22 (78.6)                   | 1.29     | 0.52–3.18      | 0.582   |
| Diabetes            | 3,799 (57.6)    | 3,776 (57.5)                | 23 (82.1)                   | 2.57     | 0.97–6.81      | 0.057   |
| Observational period (years) | 2.2 (0–70) | 2.2 (0–70) | 4.4 (0–8.9) |          |                |         |
| HbA1c (%)           |                 |                             |                             |          |                |         |
| HbA1c <7.5%         | 4,865 (73.8)    | 4,851 (73.9)                | 14 (50.0)                   | 1.00     | (Reference)    |         |
| HbA1c ≥7.5%         | 1,727 (26.2)    | 1,713 (26.1)                | 14 (50.0)                   | 2.25     | 1.07–4.75      | 0.033   |
| Insulin treatment   | 1,278 (19.4)    | 1,265 (19.3)                | 13 (46.4)                   | 3.46     | 1.63–7.37      | 0.001   |

Data are n (%) or median (interquartile range). Hazard ratio (HR) was calculated for 1 unit increment or decrement in continuous variables. CI, confidence interval; HbA1c, glycated hemoglobin.

Table 2 | Multivariate analysis of association with gastric residue in all participants

| Variable          | HR   | 95% CI       | P-value |
|-------------------|------|--------------|---------|
| Model 1           |      |              |         |
| Diabetes          | 2.67 | 0.99–7.18    | 0.053   |
| Model 2           |      |              |         |
| HbA1c (%)         |      |              |         |
| HbA1c <7.5%       | 1.00 | (Reference)  |         |
| HbA1c ≥7.5%       | 2.29 | 1.08–4.82    | 0.030   |
| Model 3           |      |              |         |
| Diabetes          | 1.61 | 0.53–4.90    | 0.401   |
| Insulin treatment | 2.93 | 1.25–6.88    | 0.013   |
| Model 4           |      |              |         |
| HbA1c (%)         |      |              |         |
| HbA1c <7.5%       | 1.00 | (Reference)  |         |
| HbA1c ≥7.5%       | 1.55 | 0.69–3.50    | 0.286   |
| Insulin treatment | 2.98 | 1.31–6.82    | 0.010   |

All the models are adjusted for age and sex. Hazard ratio (HR) was calculated for 1 unit increment or decrement in continuous variables. CI, confidence interval; HbA1c, glycated hemoglobin.

Table 3 | Characteristics of diabetes patients according to the presence of gastric residue

| Variable          | Total  n = 3,799 | No gastric residue  n = 3,776 | Gastric residue (+)  n = 23 | HR       | 95% CI         | P-value |
|-------------------|-----------------|-----------------------------|-----------------------------|----------|----------------|---------|
| Age (years)       | 65 (58–71)      | 65 (58–71)                  | 63 (56–69)                  | 0.97     | 0.93–1.02      | 0.217   |
| Sex (male)        | 2,877 (75.8)    | 2,858 (75.7)                | 19 (82.6)                   | 1.44     | 0.49–4.23      | 0.508   |
| Observational period (years) | 2.8 (0–8.1) | 2.8 (0–8.1) | 4.7 (0–9.2) |          |                |         |
| HbA1c (%)         |                 |                             |                             |          |                |         |
| HbA1c <8.2%       | 2,838 (74.7)    | 2,825 (74.8)                | 13 (56.5)                   | 1.00     | (Reference)    |         |
| HbA1c ≥8.2%       | 961 (25.3)      | 951 (25.2)                  | 10 (43.5)                   | 1.98     | 0.86–4.53      | 0.107   |
| Insulin treatment | 1,278 (33.6)    | 1,265 (33.5)                | 13 (56.5)                   | 2.87     | 1.23–6.72      | 0.015   |

Data are n (%) or median (interquartile range). Hazard ratio (HR) was calculated for 1 unit increment or decrement in continuous variables. CI, confidence interval; HbA1c, glycated hemoglobin.

Table 4 | Multivariate analysis of association with gastric residue in diabetes patients

| Variable          | HR   | 95% CI       | P-value |
|-------------------|------|--------------|---------|
| Model 1           |      |              |         |
| HbA1c (%)         |      |              |         |
| HbA1c <8.2%       | 1.00 | (Reference)  |         |
| HbA1c ≥8.2%       | 1.94 | 0.84–4.51    | 0.122   |
| Model 2           |      |              |         |
| HbA1c (%)         |      |              |         |
| HbA1c <8.2%       | 1.00 | (Reference)  |         |
| HbA1c ≥8.2%       | 1.56 | 0.66–3.68    | 0.310   |
| Insulin treatment | 2.71 | 1.13–6.49    | 0.026   |

All the models are adjusted for age and sex. Hazard ratio (HR) was calculated for 1 unit increment or decrement in continuous variables. CI, confidence interval; HbA1c, glycated hemoglobin.

In summary, the present retrospective cohort study shows for the first time that undergoing insulin treatment is a risk factor for gastric residue during an esophagogastroduodenoscopy independent of age, sex and diabetes or HbA1c.
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DISCLOSURE
The authors declare no conflict of interest.

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