Characteristics and Early Hypoglycemic Medications of Patients at Risk of Progression to Type 2 Diabetes in Japan: A Retrospective Cohort Study of Health Checkup and Claims Data

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INTRODUCTION

Early interventions to improve lifestyle are important to prevent the progression of type 2 diabetes in newly diagnosed or suspected patients.1-5 If glycemic control is not achieved through lifestyle modifications in newly diagnosed patients, hypoglycemic medical therapy is prescribed.5-8 Metformin, voglibose, and acarbose have been shown to delay the progression of type 2 diabetes in patients with risk of type 2 diabetes.1

The sequences of treatment strategies are specifically defined by clinical guidelines. For example, the American Diabetes Association (ADA) defines prediabetes as a condition necessitating the initiation of early intervention to prevent disease progression.2 First, physicians recommend that patients with prediabetes should modify their lifestyle, including diet and exercise habits. If lifestyle intervention is ineffective, metformin is prescribed to patients with prediabetes with a body mass index (BMI) greater than 35 kg/m², those younger than 60 years of age, or women with prior gestational diabetes mellitus.2,9

In Japan, the Japan Diabetes Society similarly defines impaired glucose tolerance (IGT) as the criterion for early intervention via both lifestyle modifications and medical therapy. Focusing on metabolic syndrome, which is the stage before lifestyle-related diseases, a new program to provide specific health checkups and guidance was started in 2008.10,11 Patients at risk of progression to type 2 diabetes, such as those with IGT, are recommended to visit a clinic to get a diagnosis. When patients visit the clinic, physicians first recommend that patients with IGT modify their lifestyles; subsequently, after a cycle of 3-6 months of follow-up medical checks, medical therapy is initiated if necessary.11 The period of follow-up following lifestyle interventions is not recommended by the guidelines, but there is evidence supporting the efficacy of 1-4 years of lifestyle intervention for preventing progression to type 2 diabetes in patients with IGT.11

Surveys of actual medical agents are important to gauge the suitability of early hypoglycemic medical therapy. As patients at risk of progression to type 2 diabetes are not specified by claims data, early medications have not been investigated in primary care settings in Japan. However, data from the Japanese Specific Health Checkup and Specific Health Guidance program enabled us to specify and characterize patients at risk of progression to type 2 diabetes. Thus, by tracking data from health checkup to health service claims, we were able to analyze patient characteristics and prescribe early hypoglycemic medications.

This study had two objectives. First, we assessed the characteristics of patients at risk of progression to type 2 diabetes in Japan by comparing individuals with early prescribed medications and those without medications. Second, we evaluated...
early medications among patients at risk of progression to type 2 diabetes based on patients’ characteristics.

MATERIALS AND METHODS

Data Source We used data from insurance claims and health checkups provided by the JMDC. The JMDC contracts various health insurers across Japan to collect insurance claims and health checkup results from workers and their family members annually.

In this study, we obtained a data package comprising 245868 claims (n = 190507; male:female 117943:72564) and 106984 health checkup records (n = 106984; male:female 76909:30075) for patients who had one or more medical claims related to diabetes between April 2005 and March 2015 (Fig. 1). The claims data included medical procedures, diagnoses, medications, age, and sex. The health checkup data included information regarding glycated hemoglobin A1c (HbA1c) (converted from the Japan Diabetes Society value to the National Glycohemoglobin Standardization Program value by the JMDC); fasting plasma glucose (FPG); BMI; abdominal circumference; blood pressure; levels of triglycerides, high-density lipoprotein, low-density lipoprotein, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, and serum creatinine; as well as smoking habits, drinking habits, exercise, and sleep quality.

Data Availability No additional data are available. The data used in the study were provided by the JMDC. The data license agreement does not permit the sharing of datasets with people external to the study team. Interested readers may request the data directly from the JMDC.

Study Cohort We selected the study cohort by combining claims and health checkup data using unique patient identification numbers; details are shown in Fig. 2. First, at each checkup date, we identified patients aged 40 years or older (to avoid selection bias) who had no history of being diagnosed with diabetes or receiving related medications and had FPG values of 100–125 mg/dL (5.6–6.9 mmol/L) or HbA1c values of 5.7–6.4% (39–47 mmol/mol), based on the ADA prediabetes criteria. Since a 2-h glucose tolerance test with 75 g oral glucose was not included in the checkup data, it was not used as an inclusion criterion. Next, we examined the patients’ claims data to identify clinic visits to perform diabetes tests, such as HbA1c or FPG measurements. Using the claims of the first clinic visit, we checked whether the patient had follow-up data for 1 year prior to the first clinic visit, no history of hypoglycemic medication use, no diagnosis of type 1 or any diabetes, and no diabetes-related complications such as neuropathy, Fig. 1. Flowchart of Patients Included in the Study

Using records of the first clinic visit, we checked the patients’ past (non-diabetic) records to verify that they had 1 year’s worth of data in the JMDC database.† We excluded patients from the cohort if they had a history of FPG values ≥126 mg/dL (7.0 mmol/L) or HbA1c ≥6.5% (48 mmol/mol). FPG = fasting plasma glucose, HbA1c = glycated hemoglobin A1c.

| Data package | Claims records n=190507 |
|--------------|------------------------|
| Health checkup records n=106984 |

Selection criteria were as follows:
1) Patients who were aged 40 years or older
2) FPG values of 100–125 mg/dL (5.6–6.9 mmol/L) or HbA1c values of 5.7–6.4% (39–47 mmol/mol)
3) No history of being diagnosed with diabetes or receiving related medications, n=33190

- Progress to type 2 diabetes† between first health checkup to implement the inspections of diabetes: 2484
- Within a year registered in JMDC’s database: 24120
- With any diabetes-related complications: 390
- With type 1 diabetes: 80
- Take hypoglycemic medications: 417
- Prescribed hypoglycemic medications without evaluating the presence of diabetes: 23

Patients enrolled in this study n=5676
The early-medication group n=276 (5%)
The no-medication group n=5400 (95%)
nephropathy, or retinopathy. Additionally, using the checkup data, we excluded patients from the cohort if they had a record of FPG values \( \geq 126 \text{ mg/dL} \) (7.0 mmol/L) or HbA1c \( \geq 6.5\% \) (48 mmol/mol) between any health checkup and first clinic visit for diabetes.

We divided the study cohort of patients at risk of progression to type 2 diabetes into two groups: those who initiated any hypoglycemic medication within 6 months, which is the upper limit of a cycle of 3–6 months of follow-up medical checks in patients with IGT,

\[ ^1 \] following the first clinic visit (defined as the early-medication group) and those who were not prescribed any hypoglycemic medications during the first 6 months of observation (defined as the no-medication group).

### Variables

The following patient characteristics were extracted from records of the last checkup before the first clinic visit: age, sex, FPG, HbA1c, BMI, and estimated glomerular filtration rate (eGFR). Additionally, we defined comorbidities according to their codes in the tenth revision of the International Classification of Diseases as well as according to medications taken. We also used self-reported data in the health checkup questionnaire to identify patients’ lifestyle habits such as smoking, drinking, exercise, and sleep quality. A patient was considered a current smoker if the total number of cigarettes smoked between the time the patient started smoking and the day of the health checkup was over 100 or if the patient smoked regularly every day for over 6 months or in the last month. A current drinker was defined as a patient who responded “every day” or “sometimes” in response to the question on alcohol consumption. Regarding current exercise habits, patients were asked whether they exercised for longer than 30 min for 2 or more days per week and if they consistently exercised for over 1 year. Sleep quality was measured by evaluating whether the patient had enough rest or not.

For patients who initiated medication for diabetes, we determined the agents selected as the primary monotherapy and categorized them as follows: sulfonylurea (SU), biguanide (BG), alpha-glucosidase inhibitor (\( \alpha \)-GI), thiazolidinedione (TZD; pioglitazone), glinides, dipeptidyl peptidase-4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RA), or insulin.

### Statistical Analysis

Baseline characteristics are described as means (standard deviations (S.D.s.) except for missing data. We used Fisher’s exact test or the chi-square test and the Wilcoxon test to compare categorical and continuous variables, respectively, between the early- and no-medication groups. Statistical significance was defined as \( p < 0.05 \). We calculated the proportion of each hypoglycemic agent among patients stratified by various characteristics including age, sex, BMI, and eGFR. We also compared data from the first 5 years (April 2005–March 2010) and the second 5 years (April 2010–March 2015) of the study period because physicians’ choice of hypoglycemic medications changed greatly after DPP-4i was introduced in April 2010. All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute Inc., Cary, NC, U.S.A.).

We also conducted a sensitivity analysis because early intervention should be considered for patients with FPG values of 110–125 mg/dL (6.1–6.9 mmol/L).
In Japan (higher than the ADA criteria: FPG values of 100–125 mg/dL [5.6–6.9 mmol/L]). To accomplish this, we selected patients aged 40 years and older who had FPG levels of 110–125 mg/dL (6.1–6.9 mmol/L) or HbA1c values of 5.7–6.4% (39–47 mmol/mol) at their first health checkup and performed the same analyses in this redefined patient group.

**Ethics Approval and Consent to Participate** The study was approved by the ethical committees of Meiji Pharmaceutical University (application number: 2709) and was conducted in accordance with the principles of the 2013 Declaration of Helsinki.

**RESULTS**

We identified 5676 individuals from the claims and health checkup data who met the inclusion criteria. As shown in Table 1, the mean age was 54 years (S.D.: 8); approximately 70% of the patients were men. The mean HbA1c was 5.8% (S.D.: 0.3) (41 mmol/mol [S.D.: 3.3]), and the mean FPG was 103 mg/dL (S.D.: 10) (5.7 mmol/L [S.D.: 0.6]). The mean follow-up time was 5.1 years (S.D.: 2.2). Among the eligible patients, 276 (5%) individuals initiated hypoglycemic medica-
tions within 6 months after their first clinic visit (Fig. 1).

The basic characteristics of the patients in the two groups are shown in Table 2. The proportion of individuals with FPG levels of 110–119 mg/dL (6.1–6.6 mmol/L) or HbA1c values of 6.0–6.4% (42–47 mmol/mol) was significantly greater in the early-medication group than in the no-medication group. There was also a smaller proportion of individuals with a BMI ≥ 23 kg/m² in the early-medication group than in the no-medication group. In addition, a greater proportion of individuals with a BMI ≥ 25 kg/m² occurred in the early-medication group than in the no-medication group. There were no significant differences in age and eGFR distribution between the two groups.

The proportions of individuals with hypertension, cardiovascular disorder, renal dysfunction, and liver dysfunction were significantly smaller in the early-medication group than in the no-medication group; conversely, current smoking and drinking were significantly more prevalent in the early-medication group than in the no-medication group. There was no significant difference in the proportions of individuals who exercised or had sleep problems between the groups.

The early-medication group comprised 276 individuals, 230 (83%) of whom took a single hypoglycemic agent, while 46 (17%) took two or more agents. Single hypoglycemic agents included SU for 10 individuals (4%), BG for 28 individuals (10%), a-GI for 44 individuals (16%), TZD for 18 individuals (7%), DPP-4i for 79 individuals (29%), glinides for 6 individuals (2%), and insulin for 45 individuals (16%). None of the individuals received GLP-1 RA or sodium–glucose co-transporter 2 inhibitors. Sixteen (7%) individuals received voglibose, which is approved in Japan for IGT treatment. Of the 45 individuals who used insulin as a starting medication, 39 were administered antimicrobial medications (87%; 39/45). Of these 39 individuals, 17 (44%) were administered antimicrobial medications in combination with corticosteroids; the remaining 22 individuals (56%) were treated for cancer pain and were either given potassium with insulin because of diabetic ketoacidosis or underwent growth hormone secretion tests with insulin.

The choices of hypoglycemic medications in the early-medication group are summarized in Table 3. DPP-4i and a-GI were more popular first-choice agents, covering 53% of the patients, followed by insulin and BG. Only a few patients were prescribed SU, TZD, or glinides. DPP-4i was the most commonly prescribed medication regardless of patient characteristics. BG and a-GI doses decreased with age, while DPP-4i doses increased. BG was prescribed more often for individuals with greater BMIs, whereas DPP-4i was prescribed less often. Until March 2010, a-GIs (33%) were the most prescribed hypoglycemic medication. From April 2010 onwards, DPP-4i (42%) was the most prescribed agent.

As for the sensitivity analysis, we selected a new cohort of patients under the redefined criteria as stated in Materials and Methods; a total of 4469 individuals were identified. No differences were observed in terms of patient characteristics and the proportion of the early-medication group (225 individuals;
DISCUSSION

Main Findings

In our study, approximately 5% of patients at risk of progression to type 2 diabetes—defined as prediabetes based on ADA criteria—at the health checkup initiated hypoglycemic medications of any kind within 6 months of their first clinic visit. This indicated that, except in patients with severe disease, hypoglycemic medications were started far earlier than the period recommended by the current guidelines, which showed the efficacy of preventing type 2 diabetes with 1–4 years of lifestyle interventions.1,17) The guidelines recommend lifestyle interventions, but the terms of these interventions have not been clarified for patients with risks of type 2 diabetes. Thus, it seems that patients have difficulty improving their lifestyle in clinical practice.1,2,17,18)

By comparing characteristics of individuals who were prescribed medications in the 6-month period and those who were not, this study revealed that individuals at risk of comorbidities such as hypertension, renal dysfunction, or liver dysfunction were less likely to use hypoglycemic medications. In contrast, individuals with high-risk laboratory evaluations and lifestyle factors such as high FPG, high Hba1c, smoking, or drinking were more likely to initiate hypoglycemic medications. Previous studies have reported contradictory results regarding comorbidities such as hypertension, renal dysfunction, or liver dysfunction as risks for type 2 diabetes.15,16,19) However, regarding high-risk laboratory evaluations and lifestyle factors, this study showed results similar to those of previous studies.20–28) The incidence of type 2 diabetes is lower in individuals who can control their weight or exercise daily.29) However, changes in the behavior of individuals are not easily achieved in primary care settings.30) The management of diabetes depends on patients’ self-management and support provided by medical staff.1,17,31) Furthermore, aware-

Table 2. Comparison of the Characteristics of Patients in the Early-Medication Group and No-medication Group

| Characteristic                                      | Early-medication group n (%) | No-medication group n (%) | p Value |
|----------------------------------------------------|------------------------------|---------------------------|---------|
| Sample size                                        | 276 (100)                    | 5400 (100)                |         |
| Age, years†                                        | 53 ± 8                       | 54 ± 8                    | 0.56    |
| 40–49                                              | 102 (37)                     | 1831 (34)                 |         |
| 50–59                                              | 97 (35)                      | 1951 (36)                 |         |
| 60–74                                              | 77 (28)                      | 1618 (30)                 |         |
| Sex (male)                                         | 226 (82)                     | 3756 (70)                 | <0.001  |
| Fasting plasma glucose, mg/dL (mmol/L)†            | 108 ± 11 (6.0 ± 0.6)         | 104 ± 10 (5.8 ± 0.6)      |         |
| ≤99 (5.5)                                          | 86 (31)                      | 2114 (39)                 | <0.001  |
| 100–109 (5.6–6.0)                                  | 81 (29)                      | 1768 (33)                 |         |
| 110–119 (6.1–6.6)                                  | 77 (28)                      | 2221 (23)                 |         |
| 120–125 (6.7–6.9)                                  | 32 (12)                      | 297 (6)                   |         |
| Glycated hemoglobin A1C, % (mmol/mol)†             | 6.0 ± 0.3 (42 ± 3.3)         | 5.9 ± 0.3 (41 ± 3.3)      |         |
| ≤5.6% (38)                                         | 98 (36)                      | 1642 (30)                 | <0.001  |
| 5.7–5.9% (39–41)                                   | 52 (19)                      | 1880 (35)                 |         |
| 6.0–6.4% (42–47)                                   | 126 (46)                     | 1878 (35)                 |         |
| Body mass index, kg/m²†                             | 26 ± 4                       | 24 ± 4                    |         |
| <23                                                | 79 (29)                      | 1933 (36)                 | 0.01    |
| 23 to <25                                          | 60 (22)                      | 1249 (23)                 |         |
| ≥25                                                | 137 (50)                     | 2218 (41)                 |         |
| Estimated glomerular filtration rate (mL/min/1.73 m²) |                 |                           |         |
| <30                                                | 0 (0)                        | 4 (0.2)                   | 0.98    |
| 30 ≤ 60                                            | 9 (10)                       | 165 (10)                  |         |
| 60 ≤ 90                                            | 62 (68)                      | 1174 (68)                 |         |
| >90                                                | 20 (22)                      | 371 (22)                  |         |
| Comorbidities                                      |                              |                           |         |
| Hypertension                                       | 78 (28)                      | 1971 (37)                 | 0.01    |
| Dyslipidemia                                       | 49 (18)                      | 1119 (21)                 | 0.23    |
| Cardiovascular disorder                            | 7 (3)                        | 1344 (25)                 | <0.001  |
| Obesity                                            | 122 (44)                     | 2217 (41)                 | 0.30    |
| Renal dysfunction                                  | 11 (4)                       | 685 (13)                  | <0.001  |
| Liver dysfunction                                  | 21 (8)                       | 1861 (34)                 | <0.001  |
| Lifestyle                                          |                              |                           |         |
| Current smoking                                    | 92 (37)                      | 1297 (28)                 | 0.003   |
| Current drinking                                   | 134 (64)                     | 1811 (27)                 | <0.001  |
| Not current exercising                             | 155 (76)                     | 3161 (75)                 | 0.81    |
| Not good sleep quality                             | 61 (31)                      | 1398 (36)                 | 0.19    |

†Mean ± S.D. The following patient characteristics (n = 5676) were extracted from records of the last checkup before the first clinic visit: age, sex, fasting plasma glucose, glycated hemoglobin A1c, and body mass index. We used the Fisher’s exact test or chi-square test, and Wilcoxon test to compare categorical and continuous variables, respectively, between the early-medication group and no-medication group. a) n = 247, b) n = 210, c) n = 204, d) n = 197, e) n = 4581, f) n = 4321, g) n = 4202, and h) n = 3937.
ness of progression to type 2 diabetes might be lower among individuals with probable prediabetes than among those with type 2 diabetes. Therefore, for individuals with probable prediabetes and physical disability or those with overweight, early hypoglycemic medications are possibly started based on blood glucose level or individual lifestyle factors rather than comorbidities.

Our study showed that α-GI and DPP-4i were popular first-choice agents in patients with type 2 diabetes; whether DPP-4i is effective in preventing the development of type 2 diabetes from a prediabetic state remains unclear. From 2010 (when DPP-4i was approved), DPP-4i was the most prescribed agent in patients with early stage type 2 diabetes. Prescriptions of DPP-4i for patients who were prescribed early hypoglycemic medications increased with age. SU and insulin were rarely prescribed to patients in early-stage type 2 diabetes. In a previous Japanese study, α-GI was the second most commonly prescribed hypoglycemic medication in patients with type 2 diabetes until 2009.32 From 2010 onwards, the most prescribed agent in patients with type 2 diabetes is DPP-4i.32 Trends of early hypoglycemic medication appear to be similar to trends of hypoglycemic medication for patients with type 2 diabetes. Furthermore, a previous study revealed that the types of hypoglycemic medications administered are associated with the characteristics of patients with type 2 diabetes.33 Older patients are more likely to develop severe hypoglycemia,14,35 which can potentially increase the risk of dementia.36–38 The Japanese Diabetes Society recommends that SU should be prescribed with caution to older patients.1,17 We presumed that physicians prescribed DPP-4i instead of SU to prevent the occurrence of hypoglycemia. Furthermore, the rate of BG with low risk of hypoglycemia prescriptions increased in individuals with a greater BMI, while the rate of DPP-4i prescriptions decreased. If lifestyle intervention is ineffective, BG is prescribed to patients with prediabetes in the United States.39–41 According to the guidelines of the Japan Diabetes Society, BG is recommended in obesity patients with diabetes.1,17 In Japan, the mean BMI of Japanese individuals has increased.42 Thus, the proportions of BG prescriptions for probable prediabetes might increase in the future. Insulin was prescribed to individuals with probable prediabetes, who, especially under stressful conditions, tend to have poor glycemic control that triggers diabetic ketoacidosis.43 Thus, individuals who attempted lifestyle changes, excluding some patients with acute severe type 2 diabetes, appeared to be prescribed early medications based on characteristics of individuals at risk of type 2 diabetes. With the approval of low-risk medications for hypoglycemia, individuals who do not satisfy the diagnostic criteria of type 2 diabetes in Japan might be diagnosed with type 2 diabetes and be prescribed early hypoglycemic medications.

Strengths and Limitations Although a number of studies have reported medication choices among patients with type 2 diabetes using claims data, this is the first study to report on early hypoglycemic medication for patients who were at higher risk of developing type 2 diabetes using both health checkup and claims data.

To clarify early hypoglycemic medication, we targeted patients who visited clinics for the first time for type 2 diabetes medication after receiving the results of health checkups. This database study, however, had several limitations. First, since laboratory results (such as FPG and HbA1c) were only included in checkup data, we could not confirm patients who developed type 2 diabetes and initiated antidiabetic medications between their last health checkup and first clinic visit using the claims data. Second, individuals with HbA1c levels.

### Table 3. Agents Administered to 230 Individuals Prescribed a Single Hypoglycemic Agent in the Early-Medication Group

| Overall (n = 230) | SU (n = 10) | BG (n = 28) | α-GI (n = 44) | TZD (n = 18) | Glinides (n = 6) | DPP-4i (n = 79) | Insulin (n = 45) |
|------------------|------------|------------|--------------|-------------|----------------|----------------|----------------|
| n (%)            | n (%)      | n (%)      | n (%)        | n (%)       | n (%)          | n (%)          | n (%)          |
| Age (years)      |            |            |              |             |                |                |                |
| 40–49            | 86 (100)   | 4 (5)      | 13 (15)      | 22 (26)     | 7 (8)          | 2 (2)          | 20 (23)        | 18 (21)        |
| 50–59            | 82 (100)   | 6 (7)      | 10 (12)      | 15 (18)     | 6 (7)          | 1 (1)          | 29 (35)        | 15 (18)        |
| 60–74            | 62 (100)   | 0 (0)      | 5 (8)        | 7 (11)      | 5 (8)          | 3 (5)          | 30 (48)        | 12 (19)        |
| Sex              |            |            |              |             |                |                |                |
| Male             | 188 (100)  | 7 (4)      | 22 (12)      | 34 (18)     | 12 (6)         | 6 (3)          | 69 (37)        | 38 (20)        |
| Female           | 42 (100)   | 3 (7)      | 6 (14)       | 10 (24)     | 6 (14)         | 0 (0)          | 10 (23)        | 7 (17)         |
| Body mass index (kg/m²) |        |            |              |             |                |                |                |
| <23              | 67 (100)   | 1 (1)      | 5 (7)        | 12 (18)     | 3 (4)          | 4 (6)          | 26 (39)        | 16 (24)        |
| 23 to <25        | 50 (100)   | 2 (4)      | 3 (6)        | 10 (20)     | 4 (8)          | 1 (2)          | 17 (34)        | 13 (26)        |
| ≥25              | 113 (100)  | 7 (6)      | 20 (18)      | 22 (19)     | 11 (10)        | 1 (1)          | 36 (32)        | 16 (14)        |
| Estimated glomerular filtration rate (mL/min/1.73 m²) |        |            |              |             |                |                |                |
| <30              | 0 (0)      |            |              |             |                |                |                |
| 30 ≤ 60          | 9 (100)    | 2 (22)     | 1 (11)       | 2 (22)      | 0 (0)          | 0 (0)          | 2 (22)         | 2 (22)         |
| 60 ≤ 90          | 54 (100)   | 2 (4)      | 6 (11)       | 14 (26)     | 7 (13)         | 0 (0)          | 18 (33)        | 7 (13)         |
| >90              | 16 (100)   | 0 (0)      | 1 (6)        | 4 (25)      | 4 (25)         | 1 (6)          | 3 (19)         | 3 (19)         |
| Study time-period |            |            |              |             |                |                |                |
| April 2005–March 2010 | 42 (100) | 4 (10)     | 4 (10)       | 14 (33)     | 11 (26)        | 1 (2)          | 0 (0)          | 8 (19)         |
| April 2010–March 2015 | 188 (100) | 6 (3)      | 24 (13)      | 30 (15)     | 7 (4)          | 5 (3)          | 79 (42)        | 37 (20)        |

We calculated the proportion of each hypoglycemic agent among patients stratified by various characteristics. The following patient characteristics were extracted from records of the last checkup before the first clinic visit: age, sex, body mass index and estimated glomerular filtration rate. SU = sulfonylurea, α-GI = α-glucosidase inhibitor, BG = biguanide, TZD = thiazolidinedione, DPP-4i = dipeptidyl peptidase-4 inhibitors.
between 6.0% and 7.0% (between 42 and 53 mmol/mol) at the checkup were recommended to undergo a re-examination at the clinic. However, previous research found that 69% of these patients did not visit a clinic within 3 months. Therefore, this study was only limited to patients who visited clinics after health checkups. If patients interested in health care underwent re-examination in medical institutions, they would be more likely to accept lifestyle interventions. If patients with family history of type 2 diabetes are aware of the risk of progression to type 2 diabetes, they might desire starting early antidiabetic medication. Since we could not clarify these suppositions based on patient characteristics in this study, the survey of early hypoglycemic medication may be both over- and under-estimated. Finally, we could track patients aged between 40 and 74 years by combining both the claims and health checkup data because health checkups are targeted toward this age group. In contrast, the JMDC only targets various health insurers. There is no database that targets national health insurance subscribers who have risks of type 2 diabetes, who are aged >75 years, and who did not undergo health checkups. Further research on the risk of progression to type 2 diabetes and early antidiabetic medication using a large local community cohort is necessary.

CONCLUSION

By using health checkups and claims data, we investigated whether guideline-recommended lifestyle interventions were prioritized in patients with HbA1c levels of 5.7–6.4% visiting clinics. Our study demonstrated that hypoglycemic medications were started within 6 months of the first clinic visit in at least 5% of patients with risks of type 2 diabetes before sufficient follow-up for lifestyle interventions. Furthermore, DPP-4i with low risk of hypoglycemia demonstrated to have been priority started. Since this study was limited to patients who visited clinics after undergoing health checkups, we should use more generalized epidemiological data, such as those from a large local community cohort with individuals who have risks of progression to type 2 diabetes.

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Author Contributions NK wrote the manuscript and researched the data. AS contributed to the discussion and reviewed/edited the manuscript. AK contributed to the discussion and reviewed/edited the manuscript. MA contributed to the discussion and reviewed/edited the manuscript.

Conflict of Interest The authors declare no conflict of interest.

REFERENCES

1) Tajima N, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, Goto A, Fujimoto K, Sakamoto M, Haneda M. Evidence-based practice guideline for the treatment for diabetes in Japan 2015. Diabetes Int., 6, 151–187 (2015).
2) American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care, 40 (Suppl. 1), S11–S24 (2017).
3) Zhou B, Lu Y, Hajifathalian K, et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet, 387, 1513–1530 (2016).
4) Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N. Engl. J. Med., 346, 393–403 (2002).
5) Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet, 374, 1677–1686 (2009).
6) Kawamori R, Tajima N, Iwamoto Y, Kashiwagi A, Shimamoto K, Kaku K. Voglibose for prevention of type 2 diabetes mellitus: a randomised, double-blind trial in Japanese individuals with impaired glucose tolerance. Lancet, 373, 1607–1614 (2009).
7) Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. Lancet, 359, 2072–2077 (2002).
8) Padwal R, Majumdar SR, Johnson JA, Vanry J, McAlistier FA. A systematic review of drug therapy to delay or prevent type 2 diabetes: Diabetes Care, 28, 336–344 (2005).
9) Aroda VR, Christophi CA, Edelstein SL, Zhang P, Herman WH, Barrett-Connor E, Delahanty LM, Montez MG, Ackermann RJ, Zhao X, Knowler WC, Ratner RE. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. J. Clin. Endocrinol. Metab., 100, 1646–1653 (2015).
10) Tamura T, Kimura Y. Specific health checkups in Japan: The present situation analyzed using 5-year statistics and the future. Biomed Eng Lett., 5, 22–28 (2015).
11) Tsujimura Y, Takahashi Y, Ishizaki T, Kuriyama A, Miyazaki K, Satoh T, Ikeda S, Kimura S, Nakayama T. Predictors of hyperglycaemic individuals who do not follow up with physicians after screening in Japan: a cohort study. Diabetes Res. Clin. Pract., 105, 176–184 (2014).
12) Kimura S, Sato T, Ikeda S, Noda M, Nakayama T. Development of a database of health insurance claims: standardization of disease classifications and anonymous record linkage. J. Epidemiol., 20, 413–419 (2010).
13) Ito C, Nishikino R, Onishi Y. Diagnosis of liver diseases among individuals with hepatic dysfunction detected by annual health checkup based on claims data in Japan. Value Health, 18, A680 (2015).
14) Seino Y, Nonjo K, Tajima N, Kadowaki T, Kashiwagi A, Ariki E, Ito C, Inagaki N, Iwamoto Y, Kasuga M, Hanafusa T, Haneda M, Ueki K. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. J. Diabetes Investig., 1, 212–228 (2010).
15) Yamada T, Fukushima M, Suzuki S, Yoshida T, Tokudome S, Jot H. Alcohol drinking may not be a major risk factor for fatty liver in Japanese undergoing a health checkup. Dig. Dis. Sci., 55, 176–182 (2010).
16) Suka M, Odajima T, Okamoto M, Sumitani M, Nakayama T, Sugimori H. Reading comprehension of health checkup reports and health literacy in Japanese people. Environ. Health Prev. Med., 19, 295–306 (2014).
17) Haneda M, Noda M, Origasa H, Noto H, Yabe D, Fujita Y, Goto A, Kondo T, Ariki E. Japanese clinical practice guideline for diabetes 2016. Diabetes Int., 9, 1–45 (2018).
18) American Diabetes Association. 2. Classification and diagnosis of diabetes. Diabetes Care, 42 (Suppl. 1), S13–S28 (2019).
19) Fujimoto WY, Boyko EJ, Hayashi T, Kahn SE, Leonetti DL, McNeely MJ, Shuman WP. Risk factors for type 2 diabetes: lessons
learned from Japanese Americans in Seattle. *J. Diabetes Investig.*, 3, 212–224 (2012).

20) Sun K, Liu D, Wang C, Ren M, Yang C, Yan L. Passive smoke exposure and risk of diabetes: a meta-analysis of prospective studies. *Endocrine*, 47, 421–427 (2014).

21) Cullmann M, Hilding A, Ostenson CG. Alcohol consumption and risk of pre-diabetes and type 2 diabetes development in a Swedish population. *Diabet. Med.*, 29, 441–452 (2012).

22) Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley RE, Zinman B. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care*, 30, 753–759 (2007).

23) Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metagression analysis of published data from 20 studies of 95783 individuals followed for 12.4 years. *Diabetes Care*, 22, 233–240 (1999).

24) Levitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch. Intern. Med.*, 164, 2447–2455 (2004).

25) Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyörälä K. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. The DECODE Study. *Diabetologia*, 47, 2118–2126 (2004).

26) Nauri A, Nakagawa T, Kawahara K, et al. Development of risk score for predicting 3-year incidence of type 2 diabetes: Japan epidemiology collaboration on occupational health study. *PLOS ONE*, 10, e0142779 (2015).

27) Tsuruta M, Adachi H, Hiray A, Fujitura Y, Imaizumi T. Association between alcohol intake and development of hypertension in Japanese normotensive men: 12-year follow-up study. *Am. J. Hypertens.*, 13, 482–487 (2000).

28) Niskanen L, Laaksonen DE, Nyyssönen K, Punnonen K, Valkonen VP, Fuentes R, Tuomilehto TP, Salonen R, Salonen JT. Inflammation, abdominal obesity, and smoking as predictors of hypertension. *Hypertension*, 44, 859–865 (2004).

29) Ökada R, Isshita K, Wakai K, Ishizaka Y, Kato K, Wada T, Watanabe K. Lower risk of progression from prediabetes to diabetes with health checkup with lifestyle education: Japan Ningen Dock study. *Nutr. Metab. Cardiovasc. Dis.*, 27, 679–687 (2017).

30) Yoon U, Kwok LL, Magkides A. Efficacy of lifestyle interventions in reducing diabetes incidence in patients with impaired glucose tolerance: a systematic review of randomized controlled trials. *Metabolism*, 62, 303–314 (2013).

31) Levesque C. Therapeutic lifestyle changes for diabetes mellitus. *Nurs. Clin. North Am.*, 52, 679–692 (2017).

32) Kohro T, Yamazaki T, Sato H, Harada K, Ohe K, Komuro I, Nagai R. Trends in antidiabetic prescription patterns in Japan from 2005 to 2011. *Int. Heart J.*, 54, 93–97 (2013).

33) Grant RW, Wexler DJ, Watson AJ, Lester WT, Cagliero E, Campbell EG, Nathan DM. How doctors choose medications to treat type 2 diabetes: a national survey of specialists and academic generalists. *Diabetes Care*, 30, 1448–1453 (2007).

34) Greco D, Pisciotta M, Gambina F, Maggio F. Severe hypoglycemia leading to hospital admission in type 2 diabetic patients aged 80 years or older. *Exp. Clin. Endocrinol. Diabetes*, 118, 215–219 (2010).

35) Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch. Intern. Med.*, 157, 1681–1686 (1997).

36) Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA*, 301, 1565–1572 (2009).

37) Yaffe K, Falvey CM, Hamilton N, Harris TB, Simonsick EM, Strotmeyer ES, Shorr RI, Metti A, Schwartz AV. Association between hypoglycemia and dementia in a biracial cohort of older adults with diabetes mellitus. *JAMA Intern. Med.*, 173, 1300–1306 (2013).

38) Feinberg I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S, Deary IJ, Frier BM, Strachan MW, Price JF. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: the Edinburgh type 2 diabetes study. *Diabetes Care*, 37, 507–515 (2014).

39) Hsu WC, Boyko EJ, Fujimoto WY, Kanaya A, Karmally W, Karter A, King GL, Look M, Maskarinec G, Misra R, Tayake-Pasi F, Arakaki R. Pathophysiological differences among Asians, native Hawaiians, and other Pacific Islanders and treatment implications. *Diabetes Care*, 35, 1189–1198 (2012).

40) UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*, 352, 854–865 (1998).

41) Avilés-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. *Ann. Intern. Med.*, 131, 182–188 (1999).

42) Kushiyama A, Yoshida Y, Kikuchi T, Suzawa N, Yamamoto M, Tanaka K, Okayasu M, Tahara T, Takao T, Onishi Y, Kawazu S. Twenty-year trend of increasing obesity in young patients with poorly controlled type 2 diabetes at first diagnosis in urban Japan. *J. Diabetes Investig.*, 4, 540–545 (2013).

43) Song R, Cao S. Prediabetes directly deteriorates into diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome triggered by acute pancreatitis: a case report illustrating a “Chicken and Egg” paradigm in Ketosis-Prone Diabetes. *Diabetes Ther.*, 9, 1377–1383 (2018).