

# Duration of diabetes and types of diabetes therapy in Japanese patients with type 2 diabetes: The Japan Diabetes Complication and its Prevention prospective study 3 (JDCP study 3)

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## Keywords

Diabetes therapy, Durability, Duration of diabetes

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## ABSTRACT

**Aims/Introduction:** To analyze the association between the duration of diabetes and selection of diabetes therapy in a large database of Japanese patients with type 2 diabetes.

**Materials and Methods:** We used the data of 5,844 patients with type 2 diabetes to evaluate the association between the duration of diabetes and types of diabetes therapy. The logistic regression model was used to analyze the association between duration of diabetes and selection of diabetes therapy, and restricted cubic spline curves were used to represent the schematic association.

**Results:** Overall, clinical characteristics of the patients were women, 39.9%; mean age, 61.4 years; median duration of diabetes, 9 years; mean glycosylated hemoglobin, 7.4% (57.0 mmol/mol); and mean body mass index, 24.5 kg/m<sup>2</sup>. Compared with the first quartile of diabetes duration, the multivariable-adjusted odds of any antidiabetic therapy (oral hypoglycemic agents or insulin) for the second, third and fourth quartiles were 2.17 (95% confidence interval [CI] 1.68–2.80; 3.39, 95% CI 2.53–4.54; 4.99, 95% CI 3.64–6.84), respectively (*P* for trend <0.001), and these associations were attenuated after adjusting possible confounders. Furthermore, those of insulin therapy were 1.48 (95% CI 1.20–1.84; 2.16, 95% CI 1.77–2.64; 4.94, 95% CI 4.04–6.04), respectively (*P* for trend <0.001). Schematic representation of restricted cubic spline curves analysis showed that a longer duration of diabetes was linearly associated with the odds of insulin therapy.

**Conclusions:** Obtained data showed that a longer duration of diabetes required complex diabetes drug regimens to be introduced to patients with type 2 diabetes.

## INTRODUCTION

A recent national survey in Japan showed that between 1997 and 2007, the number of patients with probable diabetes increased from 6.9 million to 8.9 million, whereas the number of patients with probable impaired glucose tolerance (IGT)

increased from 6.8 million to 13.2 million<sup>1</sup>. Japan has become the country with the fifth greatest number of patients worldwide<sup>2</sup>, and the burden of diabetes is large and growing in Japan. It is likely that a rapid change in lifestyle, including diet and exercise, and population demographics in Japan might continue to influence the incidence, prevalence or disease characteristics of diabetes mellitus. Therefore, it is important to periodically archive descriptive statistics of patients with

<sup>†</sup>Members of the JDCP study are listed in the appendix (supporting information Appendix S1).

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diabetes and diabetes complications to tackle the complicated problems associated with diabetes in Japan.

Type 2 diabetes is a complex metabolic disorder characterized by elevated blood glucose levels (hyperglycemia) and increased risk of developing cardiovascular disease. Insulin resistance and defects in insulin secretion are the established key factors for hyperglycemia in patients with type 2 diabetes; the latter plays a particularly important role in Japanese patients<sup>3–5</sup>, although recent studies show that a major part of the differences between Japanese and Caucasians can be explained by differences in body composition, such as body mass index (BMI)<sup>6,7</sup>. During the natural course of diabetes,  $\beta$ -cells secrete additional insulin in the early phase of insulin resistance and the insulin levels initially increase<sup>8</sup>. This increase in insulin secretion actually still represents a relative deficiency of insulin, because early in the course of the natural history,  $\beta$ -cell function starts to deteriorate. This pathophysiological decline or defect contributes to the progressive nature of the disease in long-standing type 2 diabetes. However, few studies have examined how these pathophysiological changes influence the selection of diabetes therapy in patients with long-standing type 2 diabetes in actual clinical settings. A previous cross-sectional study<sup>9</sup> showed that the prevalence of oral medication therapy or insulin therapy increased as the duration of diabetes increased, that study did not evaluate the association between the linearly increasing duration of diabetes and the selection of diabetes therapy.

The objective of the present study was to analyze the cross-sectional association between the duration of diabetes and the selection of diabetes therapy in patients with type 2 diabetes using data from the Japan Diabetes Complication and its Prevention prospective (JDCP) study in which the Japan Diabetes Society (JDS) studied the descriptive statistics of patients with diabetes and the association with diabetes complications in large-scale, hospital-based settings. We especially focused on the association between the linearly increasing duration of diabetes and the selection of diabetes therapy using a sophisticated statistical method.

## METHODS

### Patients

Patient data were derived from the baseline data of the JDCP study, a prospective cohort study of patients with diabetes led by the JDS. The details of this registry can be found elsewhere<sup>10</sup>. In brief, the present study was a prospective cohort study for evaluating the descriptive statistics of diabetic complications, and exploring the risk factors that might predict the incidence and progression of diabetic complications in Japanese patients with diabetes. Members of the JDCP study are listed in the appendix (Appendix S1).

We arbitrarily asked university hospitals, municipal hospitals and clinics throughout Japan to register patients with diabetes. Eligible subjects were those who regularly attended the participating hospitals/clinics and provided written informed

consented to participate in the present study. Inclusion criteria were as follows: (i) patients with type 2 diabetes; and (ii) patients aged  $\geq 40$  to  $< 75$  years. Patients were excluded if they: (i) could not attend the hospital or clinic regularly; (ii) had proliferative diabetic retinopathy; (iii) were undergoing dialysis; (iv) had been diagnosed with a malignant disease 5 years before registration; and (v) were judged to be ineligible for this study by an attending physician. Of 7,700 eligible patients, we finally registered 6,338 patients with type 1 or type 2 diabetes between July 2007 and September 2011. For the present study, we used the data of 5,944 patients with type 2 diabetes. This study was approved by the ethics committee and institutional review board of participating institutions.

### Data collection

The attending physician reported patient data using a prespecified paper case report form, anonymizing the data, and sent it to the registration center by post. The data of duration of diabetes and therapy for diabetes, smoking status (current smoker or not), regular alcohol intake (yes or no) and family history of diabetes were obtained from medical charts. Laboratory tests included evaluation of glycated hemoglobin (HbA1c), lipid profiles and biochemistry panel. HbA1c levels were expressed in accordance with the National Glycohemoglobin Standardization Program as recommended by the Japanese Diabetes Society<sup>11</sup>.

### Statistical analysis

We used the data of patients with diabetes whose duration of diabetes data, or therapy for diabetes data were available. Continuous variables were expressed as mean (standard deviation [SD]) or median (interquartile range) with skewed distribution data. Intergroup differences were evaluated using the one-way analysis of variance for normally distributed variables, the Wilcoxon rank-sum test with skewed distribution and  $\chi^2$  analysis for categorical variables. We analyzed the association between the duration of diabetes quartiles and using (i) any drug therapy compared with diet only therapy; or (ii) insulin therapy with or without oral hypoglycemic agent compared with oral hypoglycemic agent only/diet only therapy. For this analysis, we further excluded 83 cases whose data for diabetes duration were not available. A logistic regression analysis considering clustering within facilities was used to estimate the odds ratio (OR; 95% confidence interval [CI]) for diabetes therapy outcome with a reference category of diabetes duration category (1st quartile). The following three statistical models were used: (i) a crude model; (ii) an age- and sex-adjusted model; and (iii) a model adjusted for multivariables comprising age, sex, weight, maximum weight ever, waist circumference, BMI, systolic blood pressure, diastolic blood pressure, HbA1c, total cholesterol, creatinine, estimated glomerular filtration rate, exercise, diet therapy, past history of hypertension, myocardial infarction, cerebrovascular disease, family history of diabetes, regular alcohol intake (yes/no) and smoking status (current smoker or not). Sex, exercise, diet therapy, past history of hypertension,

history of myocardial infarction, history of cerebrovascular disease, family history of diabetes, regular alcohol intake and smoking status were put into the multivariable-adjusted model as categorical variables, and other variables were treated as continuous. Finally, we analyzed the change in the odds of using: (i) any drug therapy as compared with diet alone therapy; or (ii) insulin therapy as compared with oral hypoglycemic agent only/diet only therapy, with linearly increasing duration of diabetes. We used the logistic regression model (multivariable-adjusted model) with restricted cubic spline curves with four knots, which were at the 5th, 35th, 65th and 95th percentiles of the duration of diabetes.<sup>12, 13</sup> The number of knots was determined by comparing the Akaike information criterion of statistical models with different knots. All *P*-values were two-sided; *P* < 0.05 was considered statistically significant. All analyses were carried out using STATA/SE version 13.1 (Stata-Corp, College Station, TX, USA).

## RESULTS

Of 5,944 patients with type 2 diabetes registered to the JDCP study at baseline, we excluded 100 patients whose data for duration of diabetes or types of diabetes therapy were not available, and we used the data of 5,844 patients. The overall clinical (or patient) characteristics at baseline were as follows: women, 39.9%; mean age, 61.4 years; median duration of diabetes, 9 years; mean HbA1c, 7.4% (57.0 mmol/mol); and mean BMI, 24.5 kg/m<sup>2</sup> (Table 1). The median duration of diabetes for each quartile was 3, 7, 12 and 21 years, respectively, for the first to fourth quartiles of diabetes duration. We observed a significant difference among the categories of duration of diabetes quartiles in age, sex, types of diabetes therapy, weight, maximum weight ever, BMI, diastolic blood pressure, HbA1c, lipid profiles, creatinine levels, estimated glomerular filtration rate, diet therapy, past history of hypertension, myocardial infarction, cerebrovascular disease and family history of diabetes.

**Table 1** | Baseline characteristics of patients with type 2 diabetes that participated in the Japan Diabetes Complication and its Prevention study stratified by the duration of diabetes quartiles, men and women, aged 40–74 years

	All <i>n</i> = 5,844	Duration of diabetes quartile				<i>P</i> -value <sup>†</sup>
		1Q <i>n</i> = 1,770	2Q <i>n</i> = 1,225	3Q <i>n</i> = 1,425	4Q <i>n</i> = 1,424	
Duration of diabetes (years) <sup>‡</sup>	9 (5–15)	3 (1–4)	7 (7–8)	12 (10–14)	21 (18–25)	
Age (years)	61.4 (7.9)	59.2 (8.2)	60.6 (8.0)	61.9 (7.5)	64.4 (6.7)	<0.001
Women (%)	39.9	41.1	42.4	40.9	36.4	0.001
Types of diabetes therapy (%)						
Diet alone	10.5	19.8	9.4	6.0	4.1	<0.001
Oral hypoglycemic agents	62.0	63.9	69.3	65.9	49.4	
Insulin	27.6	16.3	21.3	28.1	46.5	
Weight (kg)	63.9 (12.2)	65.5 (13.1)	64.5 (12.2)	64.0 (11.8)	61.5 (10.8)	<0.001
Maximum weight ever (kg)	70.9 (13.3)	72.1 (14.2)	70.9 (12.9)	70.8 (13.1)	69.5 (12.4)	<0.001
BMI (kg/m <sup>2</sup> )	24.5 (3.9)	25 (4.0)	24.8 (4.0)	24.6 (3.9)	23.7 (3.4)	<0.001
Waist circumference (cm)	86.4 (10.4)	87.2 (10.9)	86.9 (10.1)	86.4 (10.1)	85.0 (10.2)	<0.001
Systolic blood pressure (mmHg)	129.8 (15.1)	129.3 (15.7)	129.8 (15.3)	129.5 (14.5)	130.6 (14.7)	0.094
Diastolic blood pressure (mmHg)	74.8 (10.2)	76.1 (10.7)	75.4 (10.4)	74.5 (9.6)	72.9 (9.8)	<0.001
HbA1c (%)						
NGSP (%)	7.4 (1.3)	7.3 (1.5)	7.4 (1.1)	7.5 (1.1)	7.6 (1.1)	<0.001
IFCC (mmol/mol)	57.0 (14.2)	56.0 (16.4)	57.0 (12.0)	58.0 (12.0)	60.0 (12.0)	
Total cholesterol (mmol/L)	5.05 (0.86)	5.13 (0.89)	5.06 (0.88)	5.03 (0.81)	4.96 (0.84)	<0.001
Creatinine (μmol/L)	58.2 (22.5)	56.2 (18.7)	57.0 (21.1)	58.3 (23.3)	61.6 (26.6)	<0.001
eGFR (mL/min/1.73 m <sup>2</sup> )	77.1 (18.9)	79.6 (18.4)	78.3 (19.0)	76.5 (18.5)	73.5 (19.4)	<0.001
Diet therapy (%)	84.5	85.8	81.1	84.4	85.9	0.002
Exercise (%)	77.8	78.5	76.2	78.1	78.0	0.510
Hypertension (%)	46.8	42.7	46.6	48.6	50.4	<0.001
Myocardial infarction (%)	3.4	2.4	2.7	3.2	5.4	<0.001
Cerebrovascular disease, %	5.1	4.8	3.9	4.5	7.0	0.002
Family history of diabetes (%)	52.7	46.4	53.0	54.1	59.0	<0.001
Alcohol (%)	39.0	37.5	41.0	38.1	40.0	0.193
Current smoker (%)	37.8	37.4	38.3	36.5	39.1	0.530

Data are presented as mean and standard deviation unless otherwise specified. <sup>†</sup>*P*-value by one-way ANOVA or Wilcoxon rank-sum test. <sup>‡</sup>Median and interquartile range. eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IFCC, International Federation of Clinical Chemistry; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program; OHA, oral hypoglycemic agent.

The association between the duration of diabetes quartiles and odds of any diabetes therapy (oral medication or insulin) compared with diet therapy is shown in Table 2. Compared with the first quartile, the odds of any diabetes therapy were 2.39 (95% CI 1.88–3.03), 3.85 (95% CI 2.98–4.98) and 5.72 (95% CI 4.31–7.60), respectively, for the second to fourth quartiles with a statistically significant trend ( $P < 0.001$ ). This association was slightly attenuated after adjusting for possible confounders. Compared with the first quartile of diabetes duration, the multivariable-adjusted odds of any antidiabetic therapy (oral hypoglycemic agents or insulin) for the second, third and fourth quartiles were 2.17 (95% CI 1.68–2.80), 3.39 (95% CI 2.53–4.54) and 4.99 (95% CI 3.64–6.84), respectively ( $P$  for trend  $< 0.001$ ).

The association between the duration of diabetes quartiles and odds of insulin therapy (vs diet therapy or oral medication therapy) is shown in Table 3. Compared with the first quartile, the odds of insulin therapy were 1.39 (95% CI 1.15–1.69), 2.01 (95% CI 1.63–2.48) and 4.47 (95% CI 3.61–5.54), respectively, for the second to fourth quartiles with a statistically significant trend ( $P < 0.001$ ). This association was rather slightly

intensified after adjusting for age and sex, and other possible confounders, and a significant trend ( $P < 0.001$ ) was maintained. The association between the linearly increasing duration of diabetes and the odds of any medication therapy showed that the odds of any medication therapy gradually increased with 15–20 years of diabetes duration; however, the slope became dull after 20 years (Figure 1a). The association between the linearly increasing duration of diabetes and the odds of insulin therapy showed that the odds of insulin therapy starts to increase at approximately 5–10 years of diabetes duration, and it continues to increase linearly thereafter (Figure 1b).

## DISCUSSION

In the current study, we showed that a longer duration of diabetes is associated with a higher risk of receiving insulin therapy in Japanese patients with type 2 diabetes using large-scale, hospital-based study led by the JDS. Logistic regression analysis with a restricted cubic spline enabled representation of a schematic linear association between the duration of diabetes and the odds of selecting the insulin therapy, possibly representing the pathophysiological progressive nature of type 2 diabetes.

**Table 2** | Odds ratio of diabetes medication therapy (vs diet only) for each diabetes duration quartiles

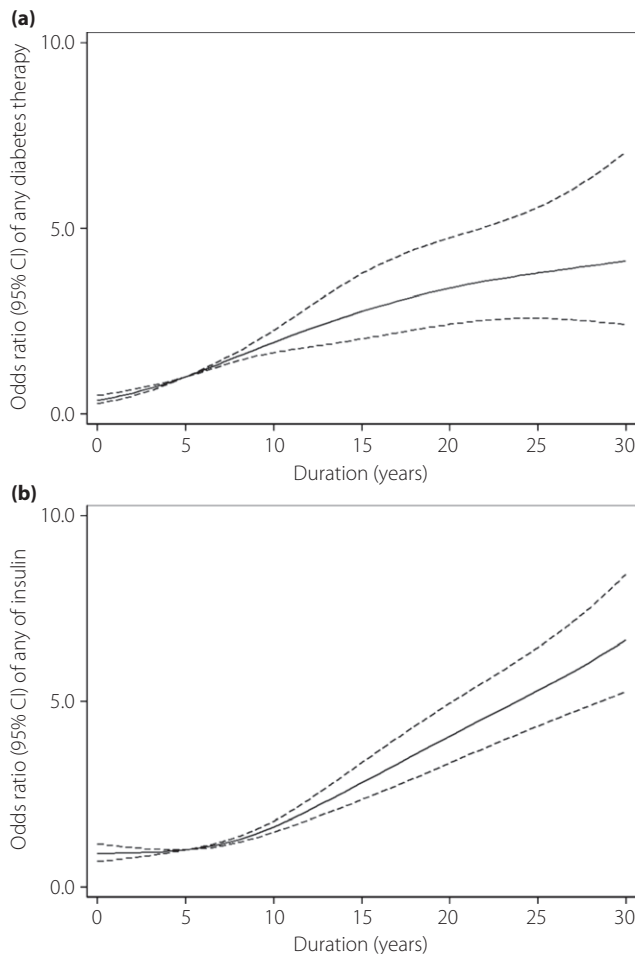
	Duration of diabetes quartiles				<i>P</i> -value for trend
	First quartile <i>n</i> = 1,770	Second quartile <i>n</i> = 1,225	Third quartile <i>n</i> = 1,425	Fourth quartile <i>n</i> = 1,424	
Median duration of diabetes, years (IRQ)	3 (1–4)	7 (7–8)	12 (10–14)	21 (18–25)	
Any drug therapy, <i>n</i> (%)	1,419 (80.2)	1,100 (90.6)	1,339 (94.0)	1,365 (95.9)	
Odds ratio of any drug therapy (95% CI)					
Crude model	Ref	2.39 (1.88–3.03)	3.85 (2.98–4.98)	5.72 (4.31–7.60)	<0.001
Age- and Sex-adjusted model	Ref	2.47 (1.95–3.14)	4.13 (3.20–5.34)	6.59 (4.91–8.84)	<0.001
Multivariable-adjusted model <sup>†</sup>	Ref	2.17 (1.68–2.80)	3.39 (2.53–4.54)	4.99 (3.64–6.84)	<0.001

<sup>†</sup>Adjusted for age, sex, weight, maximum weight ever, waist circumference, body mass index, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, total cholesterol, creatinine, estimated glomerular filtration rate, exercise, diet therapy, hypertension, myocardial infarction, cerebrovascular disease, family history of diabetes, alcohol and smoking status. CI, confidence interval; IRQ, interquartile range; Ref, reference.

**Table 3** | Odds ratio of insulin therapy (vs diet only or oral diabetes medication) for each diabetes duration quartiles

	Duration of diabetes quartiles				<i>P</i> -value for trend
	First quartile <i>n</i> = 1,770	Second quartile <i>n</i> = 1,225	Third quartile <i>n</i> = 1,425	Fourth quartile <i>n</i> = 1,424	
Median duration of diabetes, years (IRQ)	3 (1–4)	7 (7–8)	12 (10–14)	21 (18–25)	
Insulin therapy, <i>n</i> (%)	288 (16.3)	261 (21.3)	400 (28.1)	622 (46.5)	
Odds ratio of insulin therapy (95% CI)					
Crude model	Ref	1.39 (1.15–1.69)	2.01 (1.63–2.48)	4.47 (3.61–5.54)	<0.001
Age- and sex-adjusted model	Ref	1.46 (1.20–1.77)	2.21 (1.78–2.75)	5.50 (4.39–6.91)	<0.001
Multivariable-adjusted model <sup>†</sup>	Ref	1.48 (1.20–1.84)	2.16 (1.73–2.70)	4.94 (3.90–6.25)	<0.001

<sup>†</sup>Adjusted for age, sex, weight, maximum weight ever, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, glycated hemoglobin, total cholesterol, creatinine, estimated glomerular filtration rate, exercise, diet therapy, hypertension, myocardial infarction, cerebrovascular disease, family history of diabetes, alcohol, and smoking status. IRQ, interquartile range; Ref, reference.



**Figure 1** | (a) Odds ratio curve for the association between linearly increasing duration of diabetes and odds of any medication therapy (oral hypoglycemic agents or insulin) in patients with type 2 diabetes. Solid lines indicate odds ratios for any medication therapy as obtained by restricted cubic spline logistic regression with knots placed at fixed values (5th, 25th, 75th and 95th percentiles of the distribution of the duration of diabetes), and dotted lines indicate their 95% confident intervals (CI). (b) Odds ratio curve for the association between linearly increasing duration of diabetes and odds of any insulin therapy in patients with type 2 diabetes. Solid lines indicate odds ratios for insulin therapy as obtained by restricted cubic spline logistic regression with knots placed at fixed values (5th, 25th, 75th and 95th percentiles of the distribution of serum uric acid), and the dotted lines indicate their 95% CIs.

The result of the present study is consistent with a previous study. Franch-Nadal *et al.*<sup>9</sup> showed that the prevalence of oral therapy or insulin therapy increased as the duration of diabetes increased in their study to evaluate the association between cardiovascular risk factors and the duration of type 2 diabetes in Spain ( $n = 3,130$ , mean age 68.0 years, mean BMI 30.2 kg/m<sup>2</sup>). In their study, the prevalence of any medication therapy was 69.9, 82.9, 91.1 and 96.4%, respectively, for 0–5, 6–10, 11–20 and >20 years of diabetes duration; the prevalence of insulin

therapy was 10.3, 17.6, 34.2 and 53.0%, respectively, for 0–5, 6–10, 11–20 and >20 years of diabetes duration. Despite the difference in body composition or ethnicity, these figures were very similar to the results of the present study. In addition to the previous study, we have shown the graphical presentation of the association between the linearly increasing duration of diabetes and the odds of insulin therapy in patients with diabetes. The progression from normal glucose tolerance to diabetes is characterized by reductions in  $\beta$ -cell mass that lead to impaired  $\beta$ -cell function<sup>14–17</sup>, and the resulting glucotoxicity might be a known cause for the promotion of apoptosis, thus resulting in proliferative defects in  $\beta$ -cells<sup>18</sup>. Thus, a longer duration of diabetes, particularly with a poor glycemic control status, might expectedly cause impairment of  $\beta$ -cell function and increase the odds of needing insulin therapy; the present study suggests that the association might be linear. A Diabetes Outcome Progression Trial has shown the association of duration and the risk of monotherapy failure of glyburide, metformin or rosiglitazone monotherapy that were evaluated in that study. Similarly, the present study results also suggest that the odds for all drug therapies appear to increase during 15–20 years of diabetes, and become steady thereafter. Furthermore, the present study data might suggest that a certain percentage of the population diagnosed with diabetes that could endure 15–20 years without any diabetes medication, was less likely to progress thereafter, and thus, constituted the blunted slope of the association between the duration of diabetes and the odds of any medication therapy. In contrast, HbA1c levels were noted to continuously increase with the increase in the duration of diabetes despite a complex antidiabetic regimen. The obtained data, therefore, showed that the current diabetes drug therapy is not successful in terms of the durability of diabetes treatment.

In the present study, a longer duration of diabetes was associated with poor glycemic control, whereas weight, blood pressure and dyslipidemia were better controlled. This highlighted the difficulties of glycemic control against other parameters. This association was also observed in the Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation study<sup>19</sup>. In that study, the mean HbA1c levels were 7.2, 7.6, 7.8 and 7.9% in patients with a diabetes duration of 0–5 years, >5–10 years, >10–15 years and >15 years, respectively, whereas blood pressure and lipid levels decreased over time. A similar pattern was observed in the study carried out in primary care settings<sup>9</sup>. Better control of blood pressure and lipid profiles might influence the physician's attitude to certain specific quality indicators in Japan. A recent survey reported that 86.7% of Japanese physicians (non-diabetologists) measured lipid levels at least annually, and that 85.2% measure blood pressure at every visit for patients with type 2 diabetes in primary care settings<sup>20</sup>. There might be several reasons for the progressive worsening of glycemic control. First, as we stated, it could be attributed to the progressive loss of function for the pancreatic  $\beta$ -cells. Second, it might be related to the attending



physician's inertia in which therapeutic changes are sometimes introduced after several years of uncontrolled HbA1c levels<sup>21</sup>.

There were some limitations to the current study. First, this study was based on a cross-sectional design; therefore, conclusions regarding the directions of the causality of the association between the duration of diabetes and types of diabetes therapy in the current analysis cannot be drawn. Second, data were derived from the registry of Japanese patients with diabetes, thereby raising concerns regarding generalizations derived from the results, particularly for the multiethnic North American and European populations.

In conclusion, we analyzed the association between the types of diabetes therapy and characteristics of patients with type 2 diabetes, particularly focusing on the cross-sectional association between the duration of diabetes and types of diabetes therapy. A longer duration of diabetes was associated with more complex drug therapy in patients with diabetes.

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### DISCLOSURE

Naoko Tajima has served as a speaker for Abbot Japan, Takeda Pharmaceutical Company Ltd., Nippon Boehringer Ingelheim Co., Ltd. and Novo Nordisk Pharma Ltd. Rimei Nishimura has served as a speaker for Astellas Pharma Inc., Takeda Pharmaceutical Company Ltd., Eli Lilly Japan K.K., Nippon Boehringer Ingelheim Co., Ltd., Novartis Pharma K.K. and Novo Nordisk Pharma Ltd. Yasuaki Hayashino, Kazuo Izumi, Shintaro Okamura and Hideki Origasa declare no conflict of interest.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Organization of Japan Diabetes Complication and its Prevention study.