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ORIGINAL ARTICLE

Combination of disease duration-to-age at diagnosis and hemoglobin A1c-to-serum C-peptide reactivity ratios predicts patient response to glucose-lowering medication in type 2 diabetes: A retrospective cohort study across Japan (JDDM59)

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Keywords
Cohort study, Collective risk factor, Type 2 diabetes

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ABSTRACT

Aims/Introduction: Knowing the collective clinical factors that determine patient response to glucose-lowering medication would be beneficial in the treatment of type 2 diabetes. We carried out a retrospective cohort study to explore the combination of clinical factors involved in its therapeutic efficacy.

Materials and Methods: The results of cohort studies retrieved using the CoDiC® database across Japan from January 2005 to July 2018 were analyzed based on criterion that using insulin therapy indicates severe type 2 diabetes.

Results: A logistic regression analysis showed that age at diagnosis, disease duration, hemoglobin A1c (HbA1c) and serum C-peptide reactivity (CPR) at medication commencement were associated with the probability of insulin treatment. Receiver operating characteristic curve showed that these clinical factors predicted insulin treatment positivity with an area under the curve of >0.600. The area under the curve increased to 0.674 and 0.720 for the disease duration-to-age at diagnosis ratio and HbA1c-to-CPR ratio, respectively. Furthermore, area under the curve increased to 0.727 and 0.750 in the indices (duration-to-age ratio at diagnosis × 43 + HbA1c) and (duration-to-age ration at diagnosis × 21 + HbA1c-to-CPR ratio), respectively. After stratification to three groups according to the indices, monthly HbA1c levels during 6 months of treatment were higher in the upper one-third than in the lower one-third of patients, and many patients did not achieve the target HbA1c level (53 mmol/mol) in the upper one-third, although greater than fourfold more patients were administered insulin in the upper one-third.

Conclusions: The combination of disease duration-to-age at diagnosis and HbA1c-to-CPR ratios is a collective risk factor that predicts response to the medications.

INTRODUCTION

Recent data show that 85.6% of adults diagnosed with diabetes are treated with diabetes medication[1]. However, a high proportion of patients fail to reach the recommended glycemic targets for a considerable period after the diagnosis of diabetes[2,3]. Results of the National Health and Nutrition Examination Survey showed that only approximately 50% of American

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adults with diabetes are achieving a hemoglobin A1c (HbA1c) level of 53 mmol/mol (7.0%)[4]. Despite a growing understanding of diabetes and the availability of new medications and technologies, a substantial number of individuals are not at their glycemic goal[5].

Type 2 diabetes is recognized to be a heterogeneous disorder, and patients might not respond similarly to glucose-lowering therapies[6]. Many individuals with diabetes have multiple parallel defects that affect several processes[7]. There is a multiplicity of reasons for suboptimal glycemia in type 2 diabetes patients, including a lack of appreciation of the progressive decline in β-cell failure in conjunction with misguided attempts to avoid polypharmacy or insulin therapy[8]. Therefore, we considered that knowing the collective clinical factors that determine patient response to glucose-lowering medication would be beneficial in the treatment of type 2 diabetes, and carried out a retrospective cohort study to explore the combination of clinical factors involved in its therapeutic efficacy. We used the CoDiC® database to collect data from multiple institutions across Japan[9-12], and carried out statistical analyses where insulin therapy was considered an indication of a severe status of the disease pathophysiology.

MATERIALS AND METHODS

Study design and setting

This study is part of the Japan Diabetes Clinical Data Management Study Group (JDDM) study, which is a nationwide, retrospective, multicenter study exploring the collective risk factors that would determine patient responses to glucose-lowering medications in type 2 diabetes. We analyzed data extracted from the CoDiC® database to retrieve patient records from 50 clinics or general and university-affiliated hospitals participating in JDDM. In belief, JDDM is one of the largest study groups consisting of Japanese diabetes specialists to promote clinical research on diabetes. The CoDiC® database is a large, anonymized, longitudinal, validated database, which is updated annually, and contains patient clinical information for approximately 60,000 patients in >70 institutions participating in JDDM. According to Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Ministry of Health, Labor and Welfare of Japan[13], JDDM members at each institution provided written information about the study and obtained oral informed consent from the participants, and patient anonymity was preserved. The JDDM ethics committee approved the study protocol, Approval No. JDDM2018-3.

The data from January 2005 to July 2018 were obtained from primary care settings for patients. Patients had been diagnosed with type 2 diabetes by JDDM members based on the criteria in the "Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus"[14], and had started glucose-lowering medication prescribed by the JDDM members. The clinical data were collected in the Central Analytical Center established by the JDDM on CD-R storage disks in October 2018.

Participants

We reviewed the records of 13,121 patients using Microsoft Access® and Excel® software (Microsoft Corporation, Redmond, WA, USA). Eligibility criteria included age >15 years and complete records of age at the start of glucose-lowering medication, sex, age at diagnosis of type 2 diabetes, height, bodyweight and systolic blood pressure (BP) at the start of medication, HbA1c at the start of and 6 months after medication initiation, and serum C-peptide reactivity (CPR) at the start of prescription of glucose-lowering drugs. Of the 13,121 patients who were screened, 6,112 patients were excluded because they did not meet the eligibility criteria.

Variables

Clinical data, including age at the start of glucose-lowering medication, sex, age at diagnosis of type 2 diabetes, height, bodyweight and systolic BP, were collected by the JDDM members at the first visit or at the start of medication. The age at diagnosis was determined based on an interview with the patient at the time of the first visit. Duration of diabetes was calculated by subtracting the age at diagnosis from the age at the start of glucose-lowering medication by JDDM members. Body mass index (BMI) was calculated by measured weight in kilograms divided by the square of measured height in meters (kg/m^2). Blood was collected at each visit for 6 months from the start of the treatment for HbA1c measurement. HbA1c levels were measured using high-performance liquid chromatography in each clinic or hospital. The levels were standardized at each institution according to the criteria recommended by the Japan Diabetes Society committee[15]. Serum CPR was examined before or on the day the medications commenced, with a random sampling time. CPR levels were measured by radioimmunoassay at laboratory facilities inside or outside each clinic or hospital. Plasma glucose levels and serum creatinine levels at the time of CPR measurement were examined, and the serum creatinine levels were used to calculate the estimated glomerular filtration rate (eGFR) by using the Chronic Kidney Disease Epidemiology Collaboration equation[16].

The primary end-point for the present study was optimized receiver operating characteristic (ROC) and corresponding area under the curve (AUC) values of the clinical and biochemical factors that were assessed for predicting insulin treatment. The secondary outcome was the comparison of changes in HbA1c levels during the 6 months from the start of the glucose-lowering medication by members of the JDDM and prescription content for the 6th month of the treatment between patients who appeared to be more severe and those who were mild. The prescription of the medication by the JDDM members might not have been the first prescription for some patients, especially patients who had been diagnosed earlier in life and treated with insulin. This is because patients taking insulin had a lower mean HbA1c level in the upper group than in the lower group at the start of prescription by the JDDM members (Table S1). All other clinical findings were exploratory outcomes.

Statistical analysis

Statistical analyses were carried out using the SPSS version 20 software package (IBM, Armonk, NY, USA). Clinical and biochemical characteristics were compared among the patients by using unpaired *t*-test and Fisher's exact test for categorical outcomes, as appropriate. The median and quartiles of plasma glucose and eGFR were calculated from each test value at the time of CPR measurement. To determine the clinical factors associated with the severity of this disease, we carried out statistical analyses where insulin therapy was considered an indication of a severe status of the disease pathophysiology. The association of the clinical factors with the probability of receiving insulin treatment was evaluated using a logistic regression analysis. Then, we carried out ROC analysis and estimated C-statistics (AUC values) of clinical characteristics and biomarkers for predicting insulin treatment. Response to the glucose-lowering medication and the number of patients prescribed a drug were compared between patients considered to be more severe and to be less severe by using an unpaired *t*-test, Fisher's exact test for categorical outcomes and one-way ANOVA, followed by the Tukey's multiple comparison test. Variability was expressed in terms of the standard deviation or confidence intervals, and a *P*-value of <0.05 was considered to be statistically significant in all analyses.

RESULTS

Participants

A total of 7,009 patients meeting the eligibility criteria were grouped according to the glucose-lowering medication with 6,282, 695 and 32 patients taking an oral antidiabetic drug (OAD), insulin and glucagon-like peptide-1 receptor agonist, respectively, in study 1. Medication grouping was determined based on prescriptions by JDDM members 6 months after the start of medication, regardless of the previous treatment. Because of the small number of patients taking glucagon-like peptide-1 receptor agonist alone, patients taking this drug were not analyzed. Of the patients taking insulin, 340 patients received insulin alone, whereas the others also received an OAD, glucagon-like peptide-1 receptor agonist or both. In study 2, 1,043 patients examined for serum CPR among the cases included in study 1 were grouped according to the glucose-lowering medication with 864 and 179 patients taking OAD and insulin, respectively. The glucose-lowering medication was continued by members of the JDDM from the start of taking the medication to the date of data collection at the Central Analytical Center.

In study 1, the age at the start of medication was slightly higher, the age at diagnosis of type 2 diabetes was lower, disease duration was longer, BMI was lower, BP was higher, and HbA1c levels at the start of and 6 months after the initiation of medication were higher in patients taking insulin than in patients taking OAD (Table 1). In study 2, the age at diagnosis was lower, duration was longer, BP was higher, HbA1c levels were higher and serum CPR was lower in patients taking insulin than in patients taking OAD. The median (first quartile–third quartile) plasma glucose level and eGFR at CPR measurement were 9.7 mmol/L (7.6–12.7 mmol/L), 175 mg/dL (136–228 mg/dL) and 77.4 mL/min/1.73 m^2 (68.9–86.5 mL/min/1.73 m^2; n = 704), respectively.

Logistic regression analysis, and ROC curves and AUCs

In study 1, the age at diagnosis, disease duration and HbA1c level at the start of medication were associated with the probability of receiving insulin treatment, whereas the age at the start of medication, sex and BP were slightly associated, and BMI was not associated (Table 2). ROC curves and AUC values showed that 1/age at diagnosis, disease duration and HbA1c levels predicted insulin treatment positivity (Figure 1). The analyses were further carried out using factors combined with selected factors of which AUC values were >0.600. The AUC increased for the disease duration-to-age at diagnosis ratio. When the HbA1c levels were included, the AUC increased for the index (duration-to-age at diagnosis + HbA1c) and further increased for (duration-to-age at diagnosis × 43 + HbA1c). The coefficient, 43, calculated from the medians of duration-to-age at diagnosis and HbA1c level was added to the "duration-to-age at diagnosis" ratio to make it equivalent to the estimation of HbA1c.

In study 2, the logistic regression analysis showed that age at diagnosis, disease duration, HbA1c and CPR levels were associated with the probability of receiving insulin treatment (Table 2). The ROC curves and AUC values showed these factors and 1/serum CPR also predicted insulin treatment positivity in patients (Figure 2). The AUC increased for the HbA1c-to-CPR ratio. When the duration-to-age at diagnosis ratio was added, the AUC increased for (duration-to-age at diagnosis + HbA1c-to-CPR) and further increased for (duration-to-age at diagnosis × 21 + HbA1c-to-CPR). The coefficient, 21, calculated from the medians of duration-to-age at diagnosis and HbA1c-to-CPR ratios was added to the "duration-to-age at diagnosis" to make it equivalent to the estimation of HbA1c-to-CPR.

Comparison of HbA1c level improvement between patients with upper and lower indices

In study 1, the patients were stratified to three groups according to (duration-to-age at diagnosis × 43 + HbA1c). The minimum value of the index was 15.7 in the upper one-third and the maximum value was 10.5 in the lower one-third. Age was higher, age at diagnosis was markedly lower, disease duration was markedly longer and HbA1c levels were higher in the upper one-third than they were in the lower one-third (Table 3). Changes in HbA1c levels and prescription content for the 6th month of the treatment were compared between patients in the upper one-third and lower one-third of the index (Figure 3a). The HbA1c level at the start of taking medication was higher in the upper than in the lower group, and the levels decreased in both patient groups (P<0.001). However,

Table 1 | Comparison between clinical characteristics in patients taking oral anti-diabetic drugs and insulin

Study 1	Total patients	Patients on OAD	Patients on INS	*P*-value
n	6,977	6,282	695	
Age (years)	61.3 ± 11.9	61.3 ± 11.7	62.5 ± 11.9	<0.01
Sex (%male)	63.0	63.4	62.1	0.507*
Age at onset (years)	53.0 ± 11.7	53.6 ± 11.5	48.3 ± 11.8	<0.001
Duration of disease (years)	8.32 ± 8.32	7.64 ± 7.63	14.0 ± 10.9	<0.001
BMI	25.0 ± 4.3	25.4 ± 4.2	24.5 ± 4.1	<0.001
Syst BP (mmHg)	130 ± 17	130 ± 16	133 ± 20	<0.001
HbA1c at start (%)	7.81 ± 1.42	7.68 ± 1.25	8.59 ± 2.01	<0.001
(mmol/mol)	61.5 ± 15.0	60.5 ± 13.7	70.5 ± 22.1	<0.001
HbA1c after 6 months (%)	6.99 ± 0.87	6.93 ± 0.78	7.45 ± 1.16	<0.001
(mmol/mol)	52.8 ± 9.2	52.3 ± 8.6	58.0 ± 12.7	<0.001
Study 2				
n	1,043	864	179	
Age (years)	62.6 ± 11.6	62.6 ± 11.7	63.1 ± 11.2	0.338
Sex (%male)	61.5	60.9	64.2	0.448*
Age at onset (years)	53.2 ± 11.9	54.1 ± 11.7	49.1 ± 11.8	<0.001
Duration of disease (years)	9.40 ± 8.85	8.4 ± 8.1	13.8 ± 10.6	<0.001
BMI	24.7 ± 4.2	24.8 ± 4.1	24.3 ± 4.4	0.074
Syst BP (mmHg)	133 ± 18	133 ± 17	137 ± 22	<0.05
HbA1c at start (%)	8.09 ± 1.60	7.93 ± 1.47	8.83 ± 1.94	<0.001
(mmol/mol)	64.9 ± 17.5	63.3 ± 16.2	73.0 ± 21.3	<0.001
Serum CPR (ng/mL)	3.09 ± 2.03	3.28 ± 2.05	2.20 ± 1.67	<0.001
HbA1c after 6 months (%)	7.10 ± 0.88	7.00 ± 0.80	7.57 ± 1.11	<0.001
(mmol/mol)	54.1 ± 9.7	53.1 ± 8.8	59.3 ± 12.2	<0.001

xml:id="jdi13558-note-0001">**P*-value, compared between patients taking oral anti-diabetic drugs and insulin by the χ^2-test. Data are the mean ± standard deviation. *P*-value, compared between patients taking oral anti-diabetic drugs and insulin by an unpaired *t*-test. BMI, body mass index; CPR, C-peptide reactivity; HbA1c, hemoglobin A1c; INS, insulin; OAD, oral anti-diabetic drug; Syst BP, systolic blood pressure.

monthly HbA1c levels of patients during medication administration were markedly higher in the upper one-third than in the lower one-third, and many patients did not achieve the target HbA1c level, 53 mmol/mol (7.0%), in the upper one-third. The number of patients prescribed insulin was greater than fivefold more in the upper one-third during medication administration than they were in the lower one-third. Dipeptidyl peptidase-4 inhibitor and sulfonylurea were prescribed considerably more to the upper one-third and metformin was mostly prescribed to the lower one-third.

In study 2, the patients were stratified to three groups according to (duration-to-age at diagnosis × 21 + HbA1c-to-CPR). The minimum value of the index was 8.84 in the upper one-third and the maximum value was 4.46 in the lower one-third. Age was higher, age at diagnosis was markedly lower, disease duration was markedly longer, HbA1c levels were slightly higher and CPR was markedly lower in the upper one-third 3 (Table 4). As shown in Figure 3b, the HbA1c level at the start of medication was slightly higher in the upper than in the lower group, and the levels reduced in both patient groups ($P < 0.001$). However, monthly HbA1c levels from 2 months after the start of medication were markedly higher in the upper one-third than in the lower one-third. Furthermore, greater than fourfold more patients were administered insulin in the upper one-third during drug treatment than in the lower one-third, whereas the number of patients prescribed metformin, dipeptidyl peptidase-4 inhibitor and sulfonylurea did not differ between the groups.

DISCUSSION

In the present study, to identify collective risk factors that would predict patient responses to glucose-lowering medication, the results of a cohort study of patients treated with these agents were analyzed based on a strategy in which insulin therapy was considered indicative of severe type 2 diabetes. Optimized ROC and corresponding AUC values of the clinical and biochemical factors selected using a logistic regression analysis assessed the accuracy for predicting insulin treatment. ROC analysis showed that age at diagnosis, disease duration, HbA1c and serum CPR at medication commencement predicted insulin treatment positivity with an AUC of >0.600. AUC increased for the disease duration-to-age at diagnosis ratio and HbA1c-

Table 2 | Relationship between the clinical characteristics and the biomarkers at the start of drug and insulin treatment evaluated by a logistic regression analysis

Term	OR (95% CI)	*P*-value
Study 1		
Intercept		<0.001
Age	1.083 (1.073–1.094)	<0.001
Sex	1.233 (1.035–1.470)	<0.05
Age at onset	0.915 (0.906–0.923)	<0.001
BMI	0.986 (0.965–1.008)	0.21
Syst BP	1.008 (1.003–1.013)	<0.01
HbA1c at start of drug	1.569 (1.489–1.653)	<0.001
Intercept		<0.001
Age	0.991 (0.982–0.999)	<0.05
Sex	1.234 (1.036–1.471)	<0.05
Duration of disease	1.094 (1.084–1.104)	<0.001
BMI	0.986 (0.965–1.008)	0.209
Syst BP	1.008 (1.003–1.013)	<0.01
HbA1c at start of drug	1.570 (1.490–1.655)	<0.001
Study 2		
Intercept		<0.001
Age	1.068 (1.045–1.091)	<0.001
Sex	0.877 (0.606–1.268)	0.484
Age at onset	0.928 (0.910–0.947)	<0.001
BMI	1.012 (0.965–1.061)	0.62
Syst BP	1.007 (0.998–1.017)	0.139
HbA1c at start of drug	1.428 (1.287–1.584)	<0.001
Serum CPR	0.697 (0.612–0.795)	<0.001
Intercept		<0.001
Age	0.991 (0.742–1.009)	0.354
Sex	0.878 (0.608–1.270)	0.491
Duration of disease	1.077 (1.056–1.099)	<0.001
BMI	1.012 (0.965–1.061)	0.621
Syst BP	1.007 (0.998–1.017)	0.136
HbA1c at start of drug	1.426 (1.286–1.581)	<0.001
Serum CPR	0.697 (0.611–0.795)	<0.001

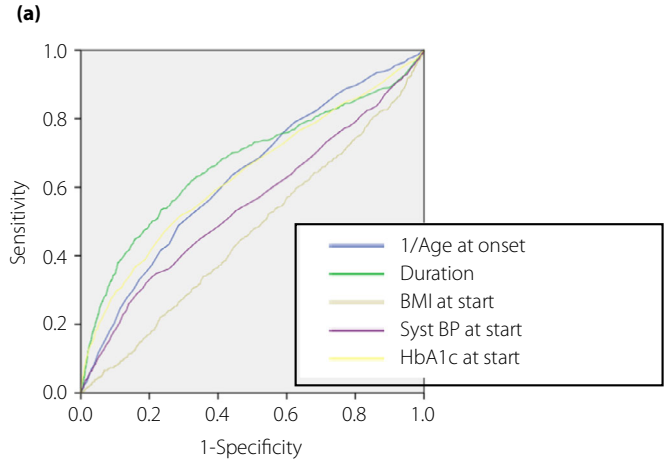
Logistic regression analysis: the response variable is insulin treatment and the independent variables in regression analysis. BMI, body mass index; CI, confidence interval; CPR, C-peptide reactivity; HbA1c, hemoglobin A1c; OR, odds ratio; Syst BP, systolic blood pressure.

to-serum CPR ratio. Furthermore, AUC increased in the indices (duration-to-age at diagnosis × 43 + HbA1c) and duration-to-age at diagnosis × 21 + HbA1c-to-CPR). More patients with higher indices had higher HbA1c levels during glucose-lowering medication, even though a considerably higher number of patients were taking insulin than those with lower indices. These findings suggest that the combination of duration-to-age at diagnosis and HbA1c-to-CPR ratios is a collective risk factor that predicts patient response to glucose-lowering medications.

Increased understanding of the pathogenesis of obesity and type 2 diabetes would not only facilitate the differentiation of responders to glucose-lowering medication from no-responders, but would also make tailored therapy a reality[17]. Individuals with hypertension are almost 2.5-fold as likely to develop type 2 diabetes as their normotensive counterparts are, and these two common chronic diseases are frequently comorbid[18,19]. However, the present study consistently showed that age at diagnosis might affect the severity of this disease more than BP and BMI. Previously, type 2 diabetes was predominantly a disease of middle-aged and older people. However, over several decades, the age at onset has decreased, and type 2 diabetes has been reported in adolescents and children worldwide[20]. The earliest abnormality in youth-onset type 2 diabetes is insulin resistance, followed by progressive β-cell failure, and the deterioration in β-cell function in young people appears to be more accelerated than that observed in adults[21]. In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study, a rapid loss of glycemic control and β-cell decline was observed in young people with type 2 diabetes[22]. The association of older age at diagnosis with a lower rate of glycemic progression was recently shown, and the prediction of time to insulin treatment has been reported to be improved by including the age at diagnosis[23]. Together with these findings, our observation indicates that age at diagnosis might be related to progression and severity of this disease.

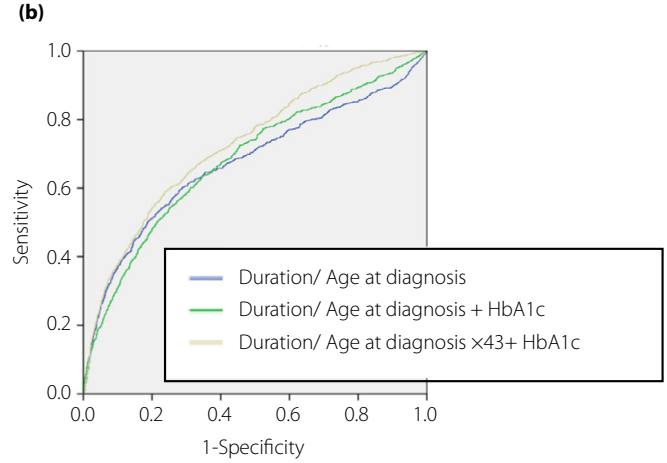
The early-onset type 2 diabetes cohort with age at diagnosis <40 years showed significantly poorer glycemic control than the cohort with age at diagnosis >40 years across all diabetes durations[24]. After patients with similar disease duration, those diagnosed with type 2 diabetes aged between 15 and 30 years were more likely to be treated with insulin than those diagnosed between 40 and 50 years[25]. A younger age at diagnosis was independently associated with higher rates of glycemic deterioration in individuals with type 2 diabetes[26]. These reports are consistent with the present data showing that the duration-to-age at diagnosis ratio predicted insulin treatment positivity with a higher AUC than each factor.

The consensus statement for the treatment of hyperglycemia in type 2 diabetes patients states that initiating dual therapy in patients with newly diagnosed type 2 diabetes who have HbA1c ≥75 mmol/mol (9%) and initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who have HbA1c ≥86 mmol/mol (10%) should be considered[27]. However, the reason for poor glycemic control is complex, and is related to the disease process itself, inadequacy of therapeutic regimens, and the attitudes of both physicians and patients[8]. Evidence that C-peptide secreted from the β-cells in equimolar concentration with insulin is not extracted by the liver has provided a firm scientific basis for the use of peripheral C-peptide concentrations as a semi-quantitative marker of β- cell secretory activity in a variety of clinical situations[28]. Because C-peptide in blood has a prolonged half-disappearance rate in normal individuals and patients with diabetes[29], random levels of CPR could approximate the level of β-cell function. A retrospective chart review to examine the relationship between baseline CPR values and future glycemic control in patients with type 2 diabetes documented that



Area under the ROC curve

Clinical characteristics and biomarkers	AUC (95% CI) (*n*=6,977)
1/Age at diagnosis	0.631 (0.609-0.653)
Duration	0.670 (0.645-0.694)
BMI at start	0.467 (0.444-0.490)
Syst BP at start	0.526 (0.525-0.574)
HbA1c at start	0.635 (0.611-0.659)



Area under the ROC curve

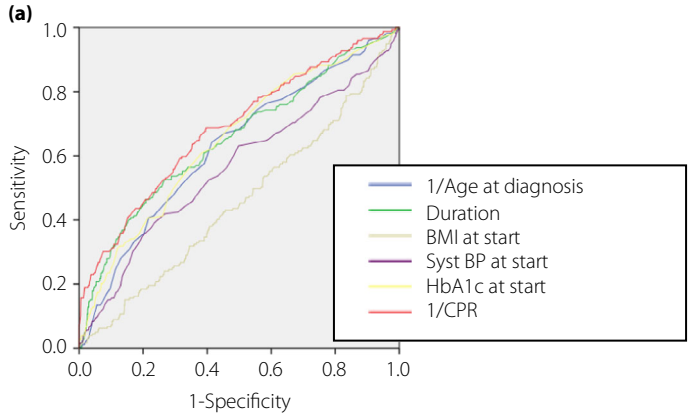
Clinical characteristics and biomarkers	AUC (95% CI) (*n*=6,977)
Duration/ Age at diagnosis	0.674 (0.649-0.698)
Duration/ Age at diagnosis + HbA1c	0.683 (0.660-0.705)
Duration/ Age at diagnosis × 43 + HbA1c	0.727 (0.707-0.748)

Figure 1 | Receiver operating characteristic (ROC) curve analysis of clinical characteristics and biochemical markers in study 1. Optimized ROC curves and areas under the curve (AUC) of the clinical and biochemical factors selected by a logistic regression analysis (see Table 2) to assess the accuracy of predicting insulin treatment. Analysis of ROC and AUC values using (a) a single factor and (b) collective factors. 1/Age at diagnosis, reciprocal of age at diagnosis; BMI, body mass index; BP, blood pressure; CI, confidence interval; HbA1c, hemoglobin A1c.

preserved β-cell function at baseline was associated with better glycemic control thereafter in patients with type 2 diabetes[30]. Because the AUC for the HbA1c-to-serum CPR ratio was higher than the AUC for HbA1c, HbA1c level in combination with C-peptide would indicate the glycemic control status that reflects the effects of β-cell dysfunction.

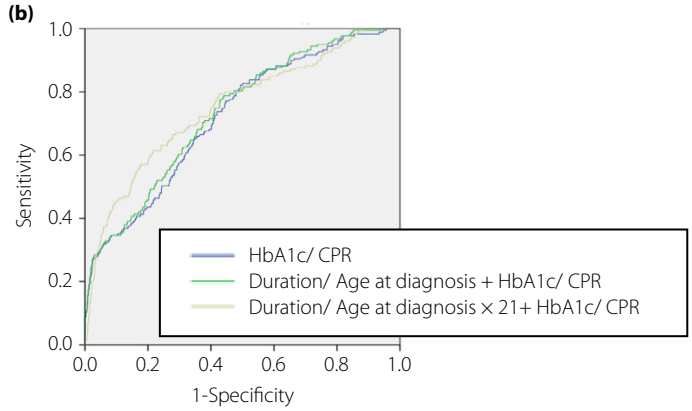
When assessing insulin production, C-peptide levels must be interpreted with caution in sampling condition and in renal impairment. Non-fasting 'random' C-peptide is likely to be the most easily carried out blood test of insulin secretion in the clinical setting, and a pragmatic approach is to measure concurrent glucose to exclude hypoglycemia (which will suppress insulin and C-peptide) with a glucose level >8 mmol/L (145 mg/dL) considered a stimulated value[31]. It seems that the suppressive effect of plasma glucose level on CPR secretion was small in the present study, because the plasma glucose levels at CPR measurement were stimulating levels in most of the patients. A finding that CPR concentrations were similar in diabetic end-stage renal disease patients and non-diabetic end-stage renal disease individuals, but were higher compared with diabetic siblings with normal renal function suggested that CPR concentrations poorly reflect pancreatic insulin synthesis once diabetes patients have end-stage renal disease[32]. A recent study to evaluate the association between baseline plasma C-peptide level and the development of type 2 diabetes indicated that eGFR was inversely associated with C-peptide levels[33]. The effect of renal function on the CPR value seems small in the present study, because most of the participants had mild impairment of renal function when evaluated by the eGFR reference value.

Consequently, the disease duration-to-age at diagnosis and HbA1c-to-serum CPR ratios, and the indices (duration-to-age at diagnosis × 43 + HbA1c) and (duration-to-age at diagnosis × 21 + HbA1c-to-CPR) promote their ability to predict the severity and patient responses to glucose-lowering medications. However, according to a rough guide of the traditional academic point system for classifying the accuracy of a diagnostic



Area under the ROC curve

Clinical characteristics and biomarkers	AUC (95% CI) (*n*=1,043)
1/Age at diagnosis	0.628 (0.582-0.673)
Duration	0.650 (0.603-0.697)
BMI at start	0.456 (0.409-0.504)
Syst BP at start	0.562 (0.512-0.612)
HbA1c at start	0.648 (0.603-0.693)
1/CPR	0.685 (0.640-0.730)



Area under the ROC curve

Clinical characteristics and biomarkers	AUC (95% CI) (*n*=1,043)
HbA1c/ CPR	0.720 (0.680-0.761)
Duration/ Age at diagnosis + HbA1c/ CPR	0.733 (0.694-0.773)
Duration/ Age at diagnosis × 21 + HbA1c/ CPR	0.750 (0.709-0.792)

Figure 2 | Receiver operating characteristic (ROC) curve analysis of clinical characteristics and biochemical markers in study 2. Optimized ROC curves and areas under the curve (AUC) of the clinical and biochemical factors selected by a logistic regression analysis (see Table 2) to assess the accuracy of predicting insulin treatment. Analysis of ROC and AUC values using (a) a single factor and (b) collective factors. 1/Age at diagnosis, reciprocal of age at diagnosis; 1/serum CPR, reciprocal of serum CPR; BMI, body mass index; BP, blood pressure; CI, confidence interval; CPR, C-peptide reactivity; HbA1c, hemoglobin A1c.

Table 3 | Comparison between clinical characteristics in patients stratified by the upper one-third and lower one-third of the index (duration-to-age at diagnosis × 43 + hemoglobin A1c) in study 1

Stratification	Case *n*	Age (years)	Age at diagnosis (years)	Duration (years)	HbA1c at start (mmol/mol)
Upper 1/3	2326	63.8 ± 11.4	46.6 ± 10.0	17.2 ± 7.9	63.1 ± 16.3
Lower 1/3	2326	59.4 ± 11.8	57.9 ± 11.5	1.5 ± 1.4	57.3 ± 10.4
P-value		<0.001	<0.001	<0.001	<0.001

The patients were stratified to three groups according to the index. Data are the mean ± standard deviation. *P*-value, compared by unpaired *t*-test. HbA1c, hemoglobin A1c.

test using ROC analysis (quoted from "Interpreting Diagnostic Tests", Tape TG, University of Nebraska Medical Center), these ratios and indices would be 'fair' at separating insulin- from non-insulin-treated patients. Pearson reviewed the recent developments that recognize the disease heterogeneity by deconvoluting the etiology of type 2 diabetes into pathophysiological processes, showing considerable variation in the phenotype of individuals with type 2 diabetes[6]. McCarthy introduced the concept of the palette model of diabetes, suggesting that many individuals with diabetes will have multiple parallel defects that affect several processes[7]. The present results in ROC analysis might suggest that diabetes is the result of more collective effects on several processes that contribute to the risk.

The cohort study presented here had some limitations. First, age at diagnosis is not always equal to age at onset in type 2 diabetes, because this disease has an insidious onset and progression. However, because the health check system has recently become comprehensive and thorough in Japan, the age of many

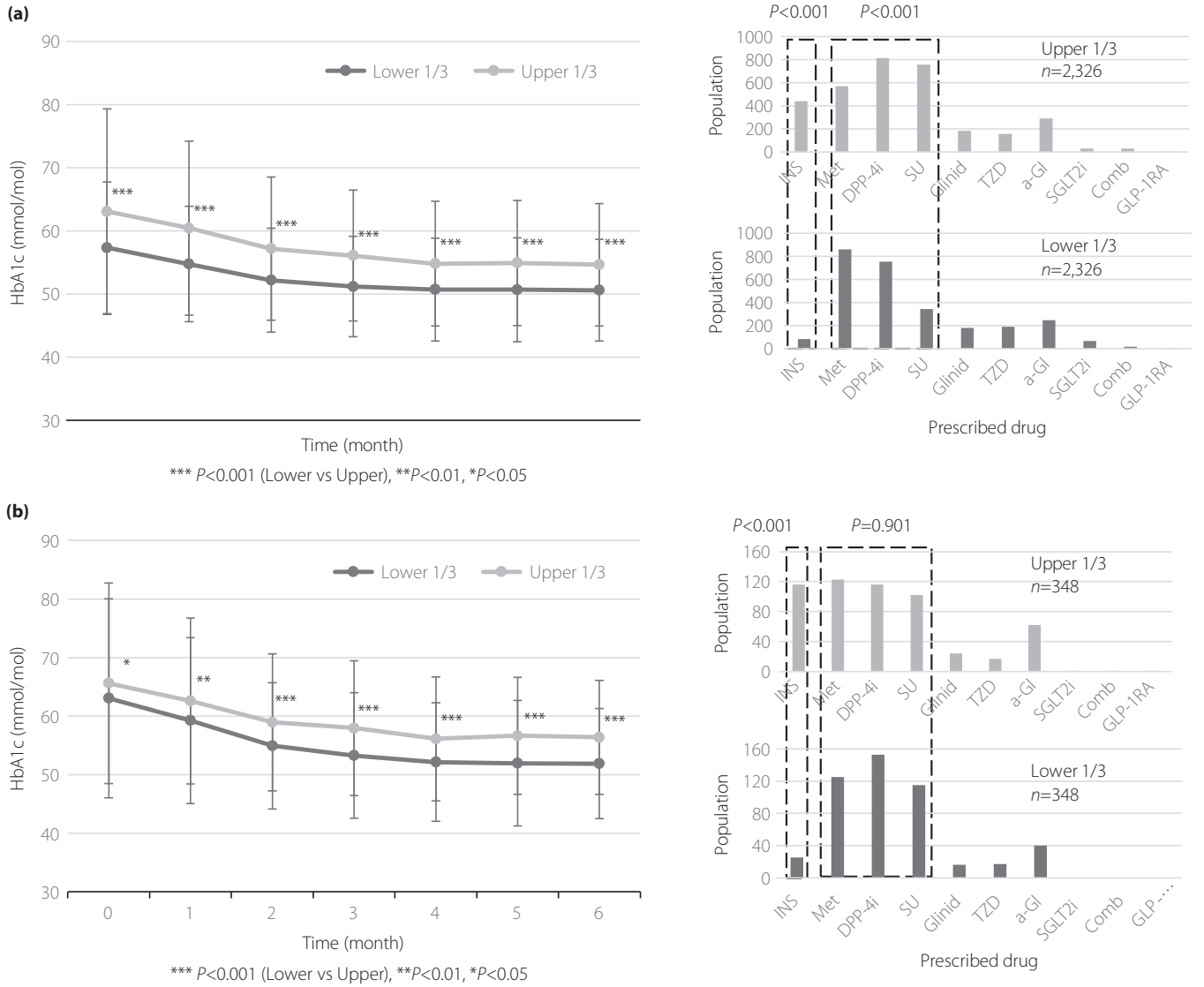


Figure 3 | Comparison of changes in hemoglobin A1c (HbA1c) and glucose-lowering medication between patients with higher and lower indices constituting clinical characteristics and biomarkers. Patients were stratified into three groups according to the indices (duration-to-age at diagnosis × 43 + HbA1c) in study 1 and (duration-to-age at diagnosis × 21 + HbA1c-to-CPR) in study 2, and changes in HbA1c and glucose-lowering medication were compared between patients of the upper one-third (upper 1/3) and lower one-third (lower 1/3). (a) Changes in HbA1c during medication administration, and population of patients taking insulin and oral anti-diabetic drugs (OAD) 6 months after medication initiation in study 1, and (b) in study 2. a-GI, alpha-glucosidase inhibitor; Comb, combination oral antidiabetic drug; DPP-4i, dipeptidyl peptidase-4 inhibitor; Glinide, metaglitinide; GLP-1 RA, glucagon-like peptide 1 receptor agonist; INS, insulin; Met, metformin; SGLT2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

of the participants at diagnosis might approximately indicate their age at onset. Second, because serum C-peptide was measured in just 15% of the patients in the present cohort study, CPR should be proactively examined in patients with type 2 diabetes at the first medical visit. Third, the treatment process of type 2 diabetes and available anti-diabetic agents have changed over the past 15 years. This study population included patients treated from 2005 to 2018; therefore, further study will be considered with this point of view. Fourth, a real-world observational study (RESPOND) is underway to provide information on patient and physician characteristics in diabetes treatment, including physician-related (specialists or non-specialists) factors[34]. These factors could affect glucose-lowering medication in patients with type 2 diabetes, and the extent and quality of diabetes education. Fifth, rare forms of diabetes resembling type 2 diabetes, including latent autoimmune diabetes in adults, maturity-onset diabetes of the young and mitochondrial diabetes, might not have been completely excluded. Autoantibodies

Table 4 | Comparison between clinical characteristics in patients stratified by the upper one-third and lower one-third of the index (duration/age at diagnosis × 21 + HbA1c-to-CPR) in study 2

Stratification	Case *n*	Age (years)	Age at diagnosis (years)	Duration (years)	HbA1c at start (mmol/mol)	CPR (ng/mL)
Upper 1/3	348	64.4 ± 11.1	46.5 ± 10.7	17.7 ± 9.5	65.6 ± 17.1	1.99 ± 1.40
Lower 1/3	348	60.7 ± 12.4	57.9 ± 11.8	2.7 ± 2.6	63.1 ± 17.0	4.59 ± 2.17
P-value		<0.001	<0.001	<0.001	<0.05	<0.001

The patients were stratified to three groups according to the index. Data are mean ± standard deviation. *P*-value, compared by unpaired *t*-test. CPR, C-peptide reactivity; HbA1c, hemoglobin A1c.

to glutamic acid decarboxylase were detected in 3.8% of Japanese patients with diabetes who were on a specific diet or OAD[35]. Tests to examine the antibodies have been readily available in Japan, and the antibodies are routinely examined in many clinics and hospitals. Thus, few cases of latent autoimmune diabetes in adults might have been included in this cohort. Maturity-onset diabetes of the young is a rare condition, accounting for 1–5% of all cases of diabetes[36]. Although maturity-onset diabetes of the young can be discriminated from type 2 diabetes, because it is inherited in an autosomal dominant fashion, some cases could not be excluded. Diabetes associated with the mitochondrial deoxyribonucleic acid 3243 (A–G) mutation is reported to occur in 0.5–2.8% of the general population of individuals with diabetes[37]. Because mitochondrial diabetes presents with maternal transmission in conjunction with bilateral hearing impairment in most carriers and the detection of mitochondrial deoxyribonucleic acid 3243 (A–G) mutation is available in Japan, few cases might have been included.

In conclusion, this work shows that disease duration-to-age at diagnosis and HbA1c-to-serum CPR ratios, and the indices (duration-to-age at diagnosis × 43 + HbA1c) and (duration-to-age at diagnosis × 21 + HbA1c-to-CPR) improve their ability to predict the patient responses to glucose-lowering medications over single factors, suggesting that these collective risk factors are effective predictors of patient responses to the medication. This information would need to be practically applied for the medications in a clinical setting, although diabetes is the result of more collective effects on several processes that contribute to the risk.

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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 | Hemoglobin A1c levels at start of glucose-lowering medication by Japan Diabetes Clinical Data Management Study Group members.