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ARTICLE

Adult-onset autoimmune diabetes identified by glutamic acid decarboxylase autoantibodies: a retrospective cohort study

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Abstract

Aims/hypothesis Patients with GAD antibodies (GADAb) showing clinical features of type 2 diabetes typically exhibit progression to an insulin-dependent state in several months or years. This condition is diagnosed as slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM) or latent autoimmune diabetes in adults, a subtype of adult-onset autoimmune diabetes. However, some patients diagnosed with adult-onset autoimmune diabetes do not progress to an insulin-dependent state. We conducted a retrospective cohort study to identify patients with non-insulin-dependent diabetes among those diagnosed with adult-onset autoimmune diabetes using measurable indicators in routine clinical practice.

Methods We surveyed data from the electronic medical records of all patients with GADAb from eight medical centres in Japan for selecting and analysing patients who matched the diagnostic criteria of SPIDDM.

Results Overall, 345 patients were analysed; of these, 162 initiated insulin therapy (insulin therapy group), whereas 183 did not (non-insulin therapy group) during the follow-up period (median 3.0 years). Patients in the non-insulin therapy group were more likely to be male and presented a later diabetes onset, shorter duration of diabetes, higher BMI, higher blood pressure levels, lower HbA_{1c} levels, lower GADAb levels and lesser antidiabetic agent use than those in the insulin therapy group when GADAb was first identified as positive. A Cox proportional hazards model showed that BMI, HbA_{1c} levels and GADAb levels were independent factors for progression to insulin therapy. Kaplan–Meier analyses revealed that 86.0% of the patients with diabetes having GADAb who presented all three factors (BMI ≥ 22 kg/m^2, HbA_{1c} < 75 mmol/mol [9.0%] and GADAb <10.0 U/ml) did not require insulin therapy for 4 years.

Conclusions/interpretation Higher BMI (≥22 kg/m^2), lower HbA_{1c} (<75 mmol/mol [9.0%]) and lower GADAb levels (<10.0 U/ml) can predict a non-insulin-dependent state for at least several years in Japanese patients with diabetes having GADAb.

Keywords Adult-onset autoimmune diabetes · Glutamic acid decarboxylase antibody · Latent autoimmune diabetes in adults · Non-insulin-dependent · Slowly progressive insulin-dependent (type 1) diabetes mellitus

Abbreviations

GADAb	GAD antibodies
LADA	Latent autoimmune diabetes in adults
ROC	Receiver operating characteristic
SPIDDM	Slowly progressive insulin-dependent (type 1) diabetes mellitus

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Introduction

Patients with GAD antibodies (GADAb) showing clinical features of type 2 diabetes in the beginning typically exhibit progression to an insulin-dependent state in several months or years. This condition is diagnosed as slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM) [1] or latent autoimmune diabetes in adults (LADA) [2, 3], a

Research in context

What is already known about this subject?

- Patients with diabetes who have GAD antibodies (GADAb) and who do not require insulin therapy at the time of diagnosis are considered to have slowly progressive insulin-dependent diabetes mellitus or latent autoimmune diabetes in adults, a subtype of adult-onset autoimmune diabetes
- There are some patients who are diagnosed as having adult-onset autoimmune diabetes but do not progress to an insulin-dependent state

What is the key question?

- Can we identify non-insulin-dependent diabetes among patients with adult-onset autoimmune diabetes using measurable indicators in routine clinical practice?

What are the new findings?

- Higher BMI (≥22 kg/m^2), lower HbA_{1c} (<75 mmol/mol [9.0%]) and lower GADAb levels (<10.0 U/ml) can predict a non-insulin-dependent state for at least several years in Japanese diabetic patients with GADAb

How might this impact on clinical practice in the foreseeable future?

- Our results indicate that patients with the above three factors (higher BMI, lower HbA_{1c} and lower GADAb levels) can be followed up without insulin therapy

subtype of adult-onset autoimmune diabetes [3, 4]. Although insulin therapy has been recommended for these patients to prevent islet beta cell failure [5–7], some patients diagnosed with adult-onset autoimmune diabetes do not show progression to an insulin-dependent state [8, 9]. In fact, GADAb was detected even in some nondiabetic individuals who did not develop diabetes over a period of 10 years [10]. These data suggest that the presence of GADAb does not necessarily indicate the development of insulin-dependent diabetes in the future. Moreover, insulin therapy could enhance hypoglycaemia [11], increase weight [12] and induce insulin antibodies in the blood [13]. Therefore, it is important to differentially identify patients with non-insulin-dependent diabetes among those diagnosed with adult-onset autoimmune diabetes and to consider treatment other than insulin therapy for these patients.

To date, several multivariate analyses have revealed the predictors of insulin requirement in patients with SPIDDM or LADA, including the presence of multiple islet autoantibodies, antithyroid peroxidase antibodies or antithyroglobulin antibodies; higher GADAb levels; lower serum C-peptide levels; lower BMI; younger age; female sex; a history of autoimmune thyroid disease; middle epitope recognition of GAD 65 antibodies; and high-risk HLA genotypes for type 1 diabetes [6, 8, 14–18]. However, the evaluation of multiple islet autoantibodies or HLA genotypes is uncommon in routine clinical practice. Furthermore, the frequency of the presence of autoantibodies other than GADAb is relatively low in patients with SPIDDM and LADA [4, 19]. Therefore, non-insulin-dependent diabetes mellitus is not included in the differential diagnosis of patients with diabetes mellitus having GADAb in clinical settings.

In the present retrospective cohort study, we aimed to identify patients with non-insulin-dependent diabetes among those diagnosed with adult-onset autoimmune diabetes using factors that have widely been used in routine clinical practice.

Methods

Study design The present multicentre retrospective cohort study was conducted at eight medical centres in Japan (Nagoya University Hospital, Anjo Kosei Hospital, Gifu Prefectural Tajimi Hospital, Nishio Municipal Hospital, Ogaki Municipal Hospital, Toki City General Hospital, Tokoname Municipal Hospital and Toyohashi Municipal Hospital). The study protocol was approved by the Ethics Committee of Nagoya University Graduate School of Medicine (No. 2014-0065). The study has been listed in the Japanese University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR: UMIN000022047; URL: https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000025417) and was performed in accordance with the ethical principles of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. Informed consent was obtained in the form of an opt-out method on the website, which was also approved by the ethics committee.

Patients We examined the electronic medical record data of all patients with measured GADAb levels between 1 May 2002 and 31 December 2015 at the eight medical centres, and a list of all GADAb-positive patients was prepared. We confirmed the type of diabetes based on diagnostic criteria [20–22] and excluded patients without diabetes as well as those with acute-onset type 1 diabetes, fulminant type 1 diabetes and diabetes related to pancreatic disease or drugs (interferon, glucocorticoid, etc.), and children aged <15 years. The diagnostic criteria of SPIDDM were as follows: presence of GADAb at some point during the clinical course of diabetes, absence of ketosis or ketoacidosis at the onset (or diagnosis) of diabetes mellitus and no insulin requirement to correct hyperglycaemia immediately after diagnosis [1]. Patients with islet cell cytoplasmic antibodies also meet the SPIDDM diagnostic criteria [1] but were excluded in this study owing to their extremely limited number. To select patients who were clinically followed up over the long term—from the diagnosis of SPIDDM to the initiation of insulin therapy determined by the attending physician's clinical discretion—the following patients were excluded: (1) those who were already treated with insulin when GADAb was first identified as positive; (2) those who could not be clinically followed up for at least 6 months; and (3) those in whom GADAb had been identified as positive before introduction of the electronic medical record. Patients with HbA_{1c} of <64 mmol/mol (8.0%) at the time of insulin initiation and those with a mean HbA_{1c} of ≥64 mmol/mol (8.0%) during the last year of the follow-up period but without insulin therapy were also excluded. The remaining patients ($n = 345$) were subjected to the analysis.

We collected the clinical variables including height, weight, BMI, blood pressure, blood biochemistry, medical history and therapy at the time of diagnosis of SPIDDM (when GADAb was first identified as positive). Furthermore, we collected the history of insulin therapy from the time of diagnosis of SPIDDM to July 2017 and obtained the exact period until the initiation of insulin therapy. Proteinuria was defined as the presence of proteinuria (≥1+ protein) on dipstick urinalysis. Diabetic retinopathy was defined as the presence of simple, preproliferative or proliferative retinopathy or any combination of these. Hypertension was defined as a systolic BP of ≥140 mmHg, a diastolic BP of ≥90 mmHg or the consumption of antihypertensive agents. Dyslipidaemia was defined as the presence of hypertriacylglycerolaemia (serum triacylglycerol: ≥1.7 mmol/l), low levels of HDL-cholesterol (<1.0 mmol/l), high levels of LDL-cholesterol (≥3.6 mmol/l) or the intake of antihyperlipidemic agents. Cerebrovascular diseases were defined as a medical history of cerebral haemorrhage or cerebral infarction. Cardiovascular diseases were defined as a medical history of coronary heart disease.

Autoantibodies GADAb levels were measured using RIA with commercially available kits (RSR, Cardiff, UK, distributed by Cosmic Corporation) in all the medical centres. GADAb-positive patients were defined as those with a GADAb level of ≥1.5 U/ml. In Japan, the assay kit for measuring GADAb was changed in December 2015 from an RIA to an ELISA. Patients who had GADAb levels measured using ELISA were excluded from this study because they did not have a sufficient follow-up period.

Statistical analysis Continuous variables were expressed as median (interquartile range). Group comparisons were performed using Fisher's exact test or Wilcoxon test as appropriate. To estimate the predictors for progression to insulin therapy, we performed multivariate analyses using the Cox proportional hazards model. Moreover, HRs and the 95% CIs were calculated. Variables with p values of <0.1 in the univariate analysis were included in the multivariate analysis. Kaplan–Meier curves were plotted, and the logrank test was performed to demonstrate the effect of each factor on the progression to insulin therapy. The event time (insulin therapy) in the Kaplan–Meier curve was rounded to the annual interval. JMP Pro version 13.0.0 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses; p values of <0.05 were considered significant.

Results

Figure 1 presents the distribution of the patients. Among 1439 patients with diabetes having GADAb, 1015 matched the diagnostic criteria of SPIDDM. Following exclusion based on the criteria, a total of 345 patients were subjected to the analysis. The median follow-up period after GADAb was first identified as positive was 3.0 years (interquartile range, 1.6–5.4). Among 345 patients, 162 initiated insulin therapy (insulin therapy group), whereas 183 did not (non-insulin therapy group) during the follow-up period.

Table 1 shows the clinical characteristics of all patients in both the insulin and non-insulin therapy groups when GADAb was first identified as positive. Patients in the non-insulin therapy group were more likely to be male and presented a later diabetes onset, shorter duration of diabetes, higher BMI, higher systolic and mean BP, lower HbA_{1c} levels, lower GADAb levels, higher triacylglycerols and lower HDL-cholesterol levels than those in the insulin therapy group. The percentage of patients who used antidiabetic agents, including a sulfonylurea agent, was significantly lower in the non-insulin therapy group than in the insulin therapy group. The percentage of patients who used antihypertensive and antihyperlipidemic agents and that of patients with diabetic complications did not significantly differ between both groups.

We performed a Cox proportional hazards model for the progression to insulin therapy during the follow-up period.

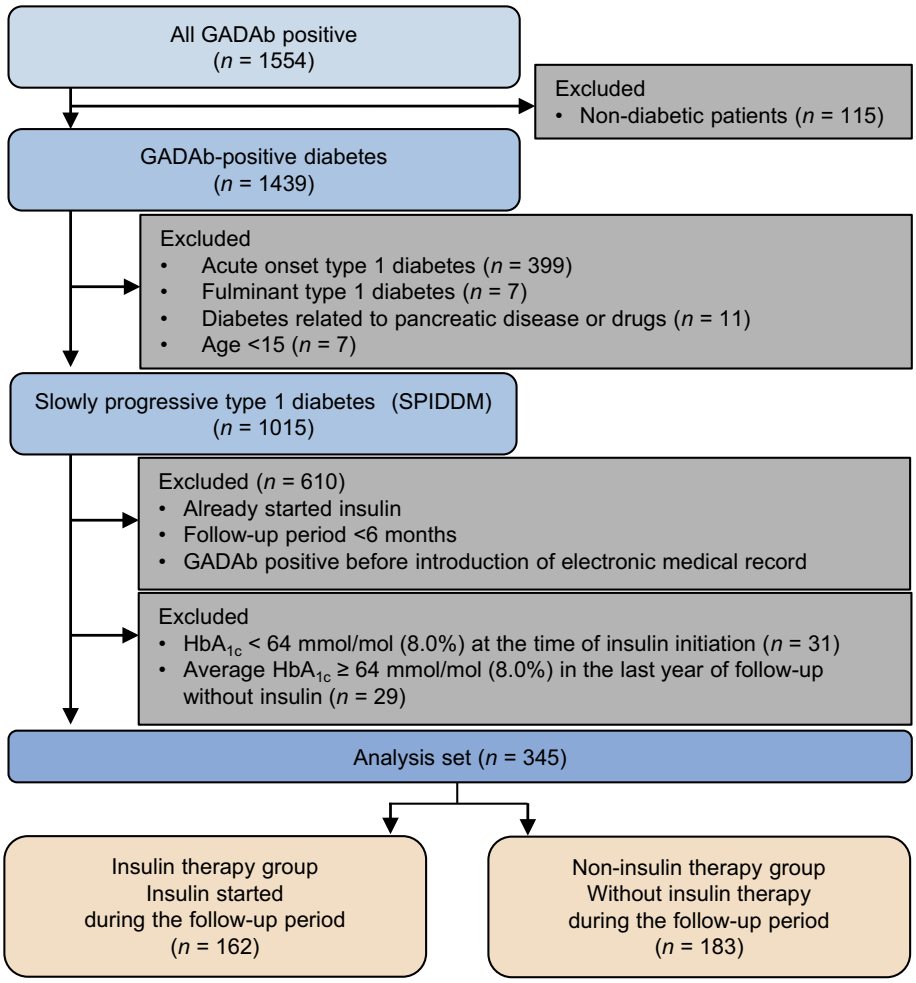

Fig. 1 Distribution of the patients

The analysis revealed that BMI (HR 0.947; 95% CI 0.906, 0.991; $p = 0.015$), HbA_{1c} levels (HR 1.009; 95% CI 1.003, 1.015; $p = 0.005$) and GADAb levels (cut-off value, 10.0 U/ml; HR 1.591; 95% CI 1.034, 2.447; $p = 0.035$) when GADAb was first identified as positive were independent factors (Table 2). Conversely, female sex ($p = 0.196$), age at diabetes onset ($p = 0.056$), duration of diabetes ($p = 0.308$), sulfonylurea agent use ($p = 0.051$) and hypertension ($p = 0.677$) did not show significant associations.

We calculated the optimal cut-off values of BMI and HbA_{1c} levels for the progression to insulin therapy using a receiver operating characteristic (ROC) curve analysis of the insulin therapy and non-insulin therapy groups (Fig. 2). The optimal cut-off level of BMI was 22 kg/m^2 (54.2% sensitivity, 81.0% specificity) and that of HbA_{1c} was 75 mmol/mol (9.0%; 83.2% sensitivity, 60.7% specificity). Kaplan–Meier curves showed that a significantly higher proportion of patients with high BMI (≥22 kg/m^2), low HbA_{1c} (<75 mmol/mol [9.0%]) or low GADAb levels (<10.0 U/ml) were not receiving insulin therapy (Fig. 3a–c). Figure 3d shows the Kaplan–Meier curves for the proportion of patients who were not receiving insulin therapy, subdivided as per the number of the three factors present (BMI ≥22 kg/m^2, HbA_{1c} < 75 mmol/mol [9.0%] and GADAb <10.0 U/ml), indicating that 86.0% of the patients with all three factors continued to not require insulin therapy with HbA_{1c} < 64 mmol/mol (8.0%) 4 years after GADAb was first identified as positive (Table 3). Positivity with all three factors predicts non-requirement of insulin therapy for 4 years with a sensitivity of 39.6%, a specificity of 94.2%, a positive predictive value of 70.4% and a negative predictive value of 82.0%.

Discussion

In the present research, we conducted a retrospective cohort study of patients diagnosed with SPIDDM to identify patients with non-insulin-dependent diabetes among those with adult-onset autoimmune diabetes using measurable indicators in routine clinical practice. To minimise the selection bias, we surveyed all patients with GADAb from multiple centres and analysed a large population of 345 patients diagnosed with SPIDDM. The study findings demonstrated that higher BMI (≥22 kg/m^2), lower HbA_{1c} (<75 mmol/mol [9.0%]) and lower

Table 1 Clinical characteristics of the study population when GADAb was first identified as positive

Characteristic	Analysis set (n=345)	Insulin therapy group (n=162)	Non-insulin therapy group (n=183)	p value
Male/female	191/154	76/86	115/68	0.003
Age (years)	60 (49–68)	59 (46–68)	61 (40–68)	0.318
Age at diabetes onset (years)	53 (43–62)	50 (40–60)	57 (46–63)	0.004
Duration of diabetes (years)	2.4 (0.1–8.6)	3.1 (0.3–10.4)	1.2 (0.0–6.9)	0.003
BMI (kg/m^2)	23.6 (20.7–27.0)	21.8 (19.4–25.0)	25.0 (22.5–28.4)	<0.001
BP (mmHg)				
Systolic BP	129 (118–144)	125 (114–138)	133 (120–149)	0.002
Diastolic BP	76 (67–84)	74 (66–82)	78 (68–85)	0.094
Mean BP	93 (85–102)	91 (84–99)	95 (88–104)	0.010
HbA_{1c} (mmol/mol)	80 (62–104)	97 (77–117)	69 (55–87)	<0.001
HbA_{1c} (%)	9.6 (8.0–11.8)	11.1 (9.3–12.9)	8.5 (7.1–10.0)	<0.001
GADAb (RIA) (U/ml)	3.3 (2.1–12.3)	6.0 (2.7–84.7)	2.6 (1.9–5.4)	<0.001
Total cholesterol (mmol/l)	5.1 (4.4–5.8)	5.0 (4.3–5.9)	5.1 (4.4–5.8)	0.865
Triacylglycerol (mmol/l)	1.3 (0.9–2.0)	1.2 (0.8–1.8)	1.5 (1.0–2.3)	0.003
HDL-cholesterol (mmol/l)	1.3 (1.0–1.5)	1.3 (1.0–1.6)	1.2 (1.0–1.4)	0.039
LDL-cholesterol (mmol/l)	3.1 (2.4–3.8)	3.1 (2.4–3.8)	3.2 (2.5–3.9)	0.080
Antidiabetic agent	135/287 (47)	90/134 (67)	45/153 (29)	<0.001
Sulfonylurea	64/287 (22)	43/134 (32)	21/153 (14)	<0.001
Glinide	14/287 (5)	11/134 (8)	3/153 (2)	0.025
Biguanide	52/287 (18)	33/134 (25)	19/153 (12)	0.009
Thiazolidine	31/287 (11)	21/134 (16)	10/153 (7)	0.021
α-Glucosidase inhibitor	55/287 (19)	42/134 (31)	13/153 (8)	<0.001
DPP-4 inhibitor	56/287 (20)	38/134 (28)	18/153 (12)	<0.001
GLP-1 receptor agonist	2/287 (1)	1/134 (1)	1/153 (1)	1.000
SGLT-2 inhibitor	2/287 (1)	1/134 (1)	1/153 (1)	1.000
Antihypertensive agent	126/334 (38)	60/156 (38)	66/178 (37)	0.822
Antihyperlipidemic agent	108/333 (32)	45/155 (29)	63/178 (35)	0.241
Proteinuria	62/322 (19)	23/151 (15)	39/171 (23)	0.091
Diabetic retinopathy	63/290 (22)	36/144 (25)	27/146 (18)	0.201
Cerebrovascular disease	24/333 (7)	9/156 (6)	15/177 (8)	0.399
Cardiovascular disease	24/333 (7)	9/156 (6)	15/177 (8)	0.399
Peripheral arterial disease	5/332 (2)	3/156 (2)	2/176 (1)	0.669
Duration of follow-up after SPIDDM diagnosis (years)	3.0 (1.6–5.4)	4.0 (2.2–7.0)	2.2(1.3–4.2)	<0.001

Data are expressed as median (interquartile range) or n (%). Regarding agent use and medical history, the number of participants for whom data were available is shown as the denominator

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium–glucose cotransporter 2

GADAb levels (<10.0 U/ml) when GADAb was first identified as positive were predictors of a non-insulin-dependent state in the future.

Yasui et al. reported that in Japanese patients with SPIDDM, BMI at diagnosis was significantly higher in patients who did not require insulin therapy for >5 years than in those who required insulin therapy within 5 years [8]. Our results are consistent with those of this study, and, using multivariate analysis, we demonstrated that BMI is a predictor of the insulin-dependent state in Japanese patients with SPIDDM. In Italian patients with LADA, low BMI (<25 kg/m^2) was reportedly a predictor for insulin requirement [16, 18]. These studies on LADA have mainly been conducted in white individuals; therefore, the differences in BMI values among the studies are likely to reflect racial backgrounds. Indeed, the mean BMI of Japanese patients with SPIDDM was 22.1 kg/m^2 [1], whereas that of Italian patients with LADA was 27.7 kg/m^2 [18]. By contrast, a cross-sectional study in Chinese individuals reported that the mean BMI of Chinese patients with LADA with high C-peptide levels was

Table 2 Results of the Cox proportional hazards model for progression to insulin therapy during the follow-up period

Variable	Univariate analysis HR (95% CI)	*p* value	Multivariate analysis HR (95% CI)	*p* value
Female	1.505 (1.105, 2.050)	0.010	1.300 (0.874, 1.929)	0.196
Age (years)	0.995 (0.984, 1.006)	0.365		
Age at diabetes onset (years)	0.988 (0.977, 0.999)	0.033	0.986 (0.972, 1.001)	0.056
Duration of diabetes (years)	1.022 (1.003, 1.040)	0.021	1.012 (0.988, 1.035)	0.308
BMI (kg/m^2)	0.909 (0.873, 0.945)	<0.001	0.947 (0.906, 0.991)	0.015
HbA_{1c} (mmol/mol)	1.016 (1.011, 1.021)	<0.001	1.009 (1.003, 1.015)	0.005
GADAb (RIA) ≥10.0 U/ml	2.349 (1.711, 3.226)	<0.001	1.591 (1.034, 2.447)	0.035
Antidiabetic agent	2.681 (1.863, 3.857)	<0.001		
Sulfonylurea	1.757 (1.221, 2.528)	0.002	1.550 (0.999, 2.403)	0.051
Glinide	2.161 (1.161, 4.022)	0.015		
Biguanide	1.565 (1.055, 2.320)	0.026		
Thiazolidine	1.651 (1.036, 2.633)	0.035		
α-Glucosidase inhibitor	2.256 (1.560, 3.263)	<0.001		
DPP-4 inhibitor	1.916 (1.311, 2.802)	<0.001		
GLP-1 receptor agonist	1.248 (0.174, 8.935)	0.825		
SGLT-2 inhibitor	1.183 (0.165, 8.462)	0.867		
Hypertension	0.724 (0.524, 1.001)	0.051	0.908 (0.576, 1.431)	0.677
Dyslipidaemia	0.847 (0.591, 1.213)	0.365		
Proteinuria	0.720 (0.462, 1.123)	0.148		
Diabetic retinopathy	1.270 (0.870, 1.853)	0.215		
Cerebrovascular disease	0.742 (0.378, 1.455)	0.385		
Cardiovascular disease	0.751 (0.383, 1.472)	0.404		
Peripheral arterial disease	1.327 (0.423, 4.163)	0.627		

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT-2, sodium–glucose cotransporter 2

24.6 kg/m^2, whereas that of those with low C-peptide levels was 21.6 kg/m^2 [23]. Therefore, our finding that BMI of 22 kg/m^2 is the cut-off value for predicting non-insulin requirement in Japanese individuals appears reasonable. The *z* score of the cut-off value of BMI (22 kg/m^2) based on the BMI data of the Japanese adult-onset diabetic population [24] was −0.60, and this value could be applied to other patients with diabetes from different racial backgrounds.

A positive correlation was reported between BMI and insulin secretion [25]; therefore, BMI may reflect the insulin secretory capacity, and patients with a low BMI may have poor insulin secretory capacity. Moreover, non-obese (BMI

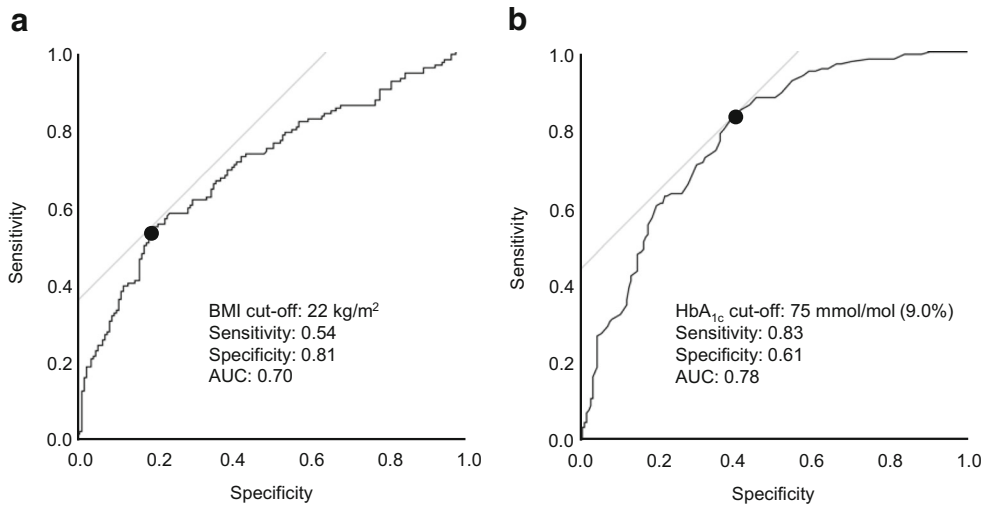

Fig. 2 Optimal cut-off values of BMI and HbA_{1c} levels for progression to insulin therapy with ROC curve analysis. (**a**) ROC curve of BMI. (**b**) ROC curve of HbA_{1c}

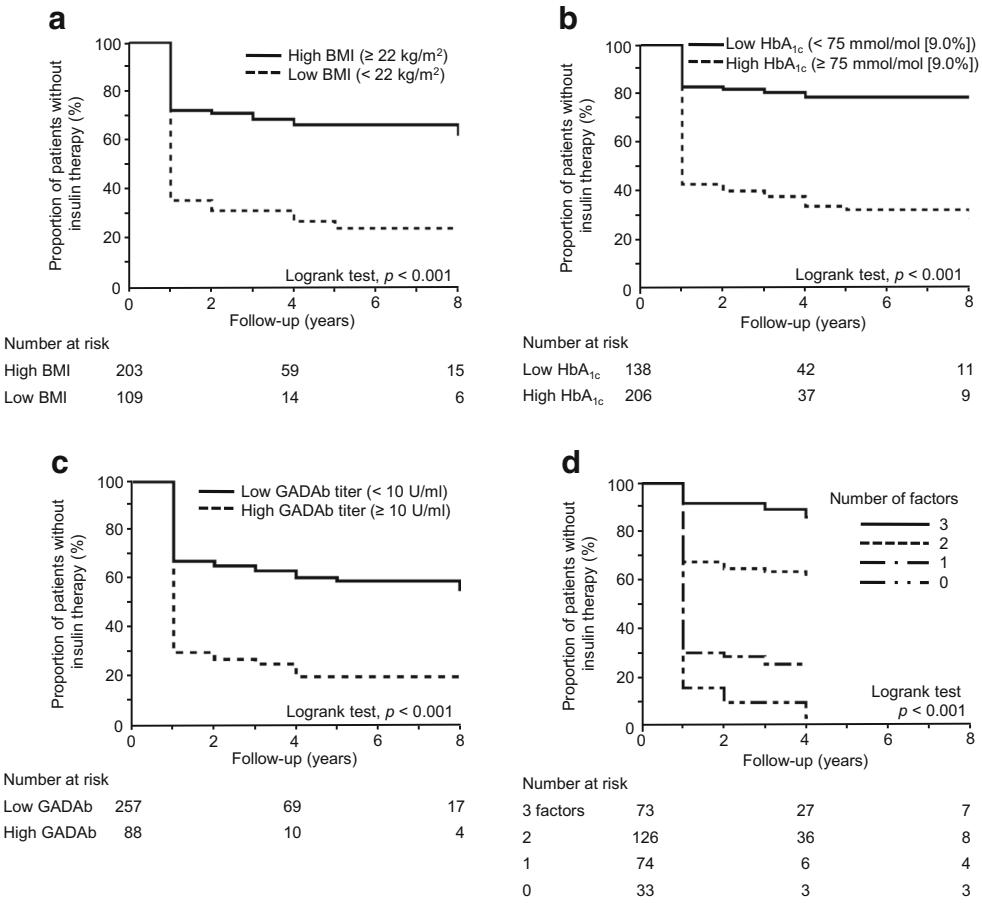

Fig. 3 Kaplan–Meier curves for the proportion of patients without insulin therapy from the time GADAb was first identified as positive. Kaplan–Meier curves for the proportion of patients without insulin therapy are subdivided as per BMI (**a**), as per HbA_{1c} level (**b**), as per GADAb level (**c**) and based on the number of the following factors: BMI ≥ 22 kg/m^2, HbA_{1c} < 75 mmol/mol (9.0%) and GADAb <10.0 U/ml (**d**)

< 22 kg/m^2) Japanese patients with SPIDDM are reportedly more likely to possess high-risk HLA genotypes for type 1 diabetes compared with obese (BMI ≥ 25 kg/m^2) patients with SPIDDM [26]. Furthermore, resistant HLA genotypes for type 1 diabetes were associated with higher BMI in patients with LADA [27, 28]. Therefore, low BMI might be associated with the genetic susceptibility to type 1 diabetes; however, further research is required to confirm this.

The frequency of the metabolic syndrome is reportedly higher in patients with LADA than in those with acute-onset type 1 diabetes [29, 30]. Moreover, patients with LADA having high C-peptide levels have a higher prevalence of the metabolic syndrome compared with those having low C-peptide levels [31]. In the present study, hypertension and dyslipidaemia, both components of the metabolic syndrome, did not contribute to progression to insulin therapy in the univariate analysis. However, because of the lack of data on waist circumference in this study, it is unclear whether the existence of the metabolic syndrome could predict non-insulin-dependent diabetes among patients with adult-onset autoimmune diabetes.

Several studies have reported the association between GADAb level and insulin dependence in patients with SPIDDM and LADA [4, 6, 8, 15–17, 32–34]. A study including a large number of patients with LADA in the United Arab Emirates reported that lower GADAb levels were associated with a longer duration to insulin therapy initiation [33], thereby suggesting a link between GADAb levels and the progression of beta cell dysfunction. In addition, several studies have emphasised the similarities in patient backgrounds between

Table 3 Association between the number of factors (BMI ≥22 kg/m^2, HbA_{1c} < 75 mmol/mol [9.0%] and GADAb <10.0 U/ml) and the proportion of patients without insulin therapy at 4 years after GADAb was first identified as positive

Number of factors	Percentage of patients without insulin therapy 4 years after GADAb was first identified as positive
0	3.0
1	25.0
2	61.6
3	86.0

LADA with low GADAb levels and type 2 diabetes [4, 18, 34]; a study from China reported that patients with low GADAb levels showed a low rate of decrease in C-peptide level, similar to patients with type 2 diabetes [34]. GADAb level of ≥10.0 U/ml has been proposed as a cut-off value [8, 15, 32], and a previous study demonstrated that early administration of small doses of insulin was more effective in preventing islet beta cell failure in Japanese patients with high GADAb levels (≥10.0 U/ml) [5]. These data are consistent with our finding that GADAb levels are significantly different between the insulin therapy and non-insulin therapy groups. In addition, GADAb level (cut-off value: 10.0 U/ml) was a significant factor for progression to insulin therapy as per the Cox proportional hazards model.

A previous study showed that patients with LADA who did not require insulin therapy during the 7 year follow-up had lower HbA_{1c} levels than those who required insulin therapy [16]. To the best of our knowledge, this is the first study to report the case of a Japanese patient with diabetes having GADAb; low HbA_{1c} levels could predict that the patient would not require insulin in the future. A plausible explanation for this is that the low HbA_{1c} level when GADAb was first identified as positive may reflect the insulin secretory capacity of the patient.

We used data on BMI, HbA_{1c} and GADAb—all measured in routine clinical practice—to demonstrate that 86.0% of the patients with all three factors (BMI ≥22 kg/m^2, HbA_{1c} < 75 mmol/mol [9.0%] and GADAb <10.0 U/ml) did not require insulin even 4 years after GADAb was first identified as positive. Therefore, based on our findings, we could predict and identify (albeit not completely) patients with diabetes having GADAb who do not require insulin therapy in routine clinical practice. Thereby, unnecessary insulin therapy may be prevented for such patients. Although age was not a predictor for the insulin-dependent state in our study, a previous study showed that the relationship among GADAb, HbA_{1c}, BMI and insulin requirement depended on patient age [17]. Therefore, to examine the predictive values for requirement of insulin therapy based on patient age, a future study that includes patients categorised according to their age group, with an adequate number of patients in each group, is warranted.

The advantage of our study is that it is a large-scale longitudinal study in patients with SPIDDM and that we could minimise selection bias by surveying all patients positive for GADAb. Conversely, this study had some limitations. First, there was a lack of data on the insulin secretory capacity, such as C-peptide. A recent consensus statement on LADA recommends repeated measurement of serum C-peptide levels and selection of treatments, such as insulin or metformin, depending on the C-peptide level [3]. Therefore, future studies are required to clarify the importance of the addition of C-peptide levels to the factors identified in this study (BMI, HbA_{1c} and GADAb) in predicting beta cell function in patients diagnosed with adult-onset autoimmune diabetes. Second, data on multiple islet autoantibodies were not analysed owing to limited data. Third, data on HLA were not available in this retrospective study. HLA genotypes susceptible to type 1 diabetes reportedly pose a high risk for developing insulin dependence in LADA [18], and genetic risk factors for type 1 diabetes were observed even in nondiabetic adults with GADAb [35]. Therefore, an analysis of the genetic backgrounds of patients diagnosed with adult-onset autoimmune diabetes who do not progress to an insulin-dependent state would be interesting. Fourth, laboratory data were measured at each facility but not at a central laboratory. Fifth, because GADAb measurement by ELISA was initiated after December 2015 in Japan, patients with GADAb identified with ELISA were not included. Sixth, considering that this was a retrospective study, prospective studies are required to confirm the efficacy of the factors identified in this study.

In conclusion, a higher BMI (≥22 kg/m^2), lower HbA_{1c} levels (<75 mmol/mol [9.0%]) and lower GADAb levels (<10.0 U/ml) could predict a non-insulin-dependent state for at least several years in Japanese patients with diabetes having GADAb. Moreover, patients who have the above-mentioned three factors could be followed up without insulin therapy.

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Contribution statement T. Onoue, MG and HA designed the study. EW, T. Kinoshita, AH, TH, MI, MF, T. Okuji, T. Kobayashi, SI, MS, HT, DH, HS and RB acquired the data. EW and T. Onoue analysed the data. EW, T. Onoue, T. Kobayashi, MG and HA interpreted the data. EW and T. Onoue wrote the first draft of the manuscript and together with all the co-authors worked collaboratively to write, discuss and review this manuscript, which was revised and edited by HA. All authors have read and approved the final manuscript. T. Onoue is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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