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# Clinical features among adult-onset type 1 diabetes, distribution of subtypes, and differences in probable and definite slowly progressive insulin-dependent diabetes mellitus: A single hospital-based study over a 13-year period

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## ABSTRACT

**Aims:** In Japan, type 1 diabetes (T1D) is classified into three subtypes based on its onset patterns; however, the proportion of each subtype remains unexplored. To elucidate the heterogeneity in adult-onset type 1 diabetes, we compared the frequencies of subtypes and clinical features by age at onset.

**Materials and Methods:** This cross-sectional, observational, single-institution study included 482 individuals (161 male) with T1D. The clinical and laboratory data, including glutamic acid decarboxylase autoantibodies, were extracted from the medical records.

**Results:** The number of adults who developed T1D decreased with age. Among all patients, 62% ($n$ = 299) had acute-onset T1D, 27% ($n$ = 131) had slowly progressive T1D (SPIDDM), and 11% ($n$ = 52) had fulminant T1D. The proportion of patients with fulminant T1D was approximately equivalent in all age groups; however, the percentage of patients with acute-onset T1D decreased from 78% in the 20–29 age group to 27% in the 70–79 age group. The proportion of patients with SPIDDM significantly increased with age, ranging from 16% in the 20–29 age group to 60% in the 70–79 age group. Among patients with SPIDDM, the prevalence of definite SPIDDM was 89%, and this prevalence did not differ based on the age at onset. Body mass index and C-peptide levels among patients with probable SPIDDM were significantly higher than those among patients with definite SPIDDM.

**Conclusions:** The proportion of adult-onset T1D subtypes differed according to the age at onset. In adult-onset T1D, some etiological differences may be based on age at onset.

## INTRODUCTION

Type 1 diabetes (T1D) has long been considered a predominantly childhood and adolescent disease; however, it can occur at any age. According to the UK Biobank data, genetically defined T1D accounted for 9.7% of all diabetes cases diagnosed within the first six decades of life. Among these, 42% were diagnosed between the ages of 31 and 60 years. The clinical characteristics of T1D were similar between individuals diagnosed at age 31–60 years and those diagnosed at 30 year of age or younger; both groups exhibited a low BMI, rapid progression to insulin therapy, and a higher risk of diabetic ketoacidosis compared to individuals presumed to have type 2

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diabetes[1]. A previous study in Japan screened 4,980 patients with adult-onset diabetes, and anti-glutamic acid decarboxylase antibody (GADAb) was detected in 188 (3.8%) patients[2]. A report from the Committee on Type 1 Diabetes of the Japan Diabetes Society indicated that among 589 adults with a history of diabetes ≤5 years, the proportion of slowly progressive T1D (SPIDDM) was 10%[3]. In other studies conducted in Japan, the positivity rate of GAD antibodies in adult patients with type 2 diabetes mellitus ranged from 3.8% to 6.6%[4,5]. Thus, it is expected that the incidence of T1D, including SPIDDM diagnosed in adulthood, is higher than previously thought.

In Japan, T1D is classified into three subtypes: acute-onset T1D, SPIDDM, and fulminant T1D[6,7]. In 2023, the diagnostic criteria for SPIDDM were revised, and new concepts of "definite SPIDDM" and "probable SPIDDM" were introduced[8,9]. Previous studies have reported the proportion of each subtype of T1D. Although 90% of childhood T1D cases have an acute onset[6,7], approximately two thirds of adult T1D cases are classified as SPIDDM, 27% as acute-onset T1D, and 6% as fulminant T1D based on the nationwide survey of fulminant T1D cases[10]. The results vary based on the age at onset. Therefore, we hypothesized that there may be differences in the proportion of subtypes based on the age at onset.

The current study aimed to investigate the frequency of subtypes and clinical features at onset among individuals with adult-onset T1D categorized by the age at disease onset as well as to elucidate the differences in the clinical characteristics at the onset of newly defined definite and probable SPIDDM.

## MATERIALS AND METHODS

### Participants

From the hospital database, we identified 1,172 new ambulatory visit Japanese patients with T1D who were >20 years old and had visited the Division of Diabetology and Metabolism at Tokyo Women's Medical University Hospital from January 1, 2003 to December 31, 2015. Patients were excluded if they were <20 years old at the time of diagnosis ($n$ = 187), had a history of diabetes for >5 years at their initial visit ($n$ = 218), had other types of diabetes ($n$ = 204), or had insufficient data and clinical course at onset ($n$ = 81). Finally, data from 482 individuals with T1D were obtained and analyzed.

### Clinical data

Data regarding the clinical course at onset (including age, sex, BMI, flu-like symptoms, digestive symptoms, hyperglycemic symptoms, consciousness, and weight reduction) and laboratory findings (including blood glucose, hemoglobin A1c [HbA1c], and fasting C-peptide levels) were extracted from patients' medical records. Blood glucose and HbA1c levels were based on data obtained at the time of diabetes diagnosis. For fasting serum C-peptide level and GADAb, the earliest available data within 1 year after diagnosis were used for fulminant T1D and acute-onset type 1 diabetes. In the case of SPIDDM, data of serum C-peptide level and GADAb from the time when GADAb positivity was first confirmed were utilized. If the diagnosis was made at another medical institution, data were extracted from referral letters or medical history obtained through interviews and recorded in the medical chart. At our institution, endogenous insulin secretion was evaluated; however, prior to the initiation of insulin therapy, serum insulin levels were measured instead of serum C-peptide levels. In such cases, fasting serum C-peptide levels were treated as missing data.

For insulin dosage, we considered values obtained within the first year after the initiation of insulin therapy except for the honeymoon period when blood glucose management became stable. Additionally, we tested for GADAb using radioimmunoassay (Cosmic Inc. Tokyo, Japan) with a cutoff value of 1.5 U/mL. In cases where GADAb was negative, IA-2 (insulinoma-associated protein-2) antibodies were measured.

T1D was diagnosed following the guidelines of the Japanese Diabetes Society, and the three subtypes of T1D were diagnosed in accordance with the recommendations of the Japan Diabetes Society Committee on Type 1 Diabetes Research[8,9,11–13]. Accordingly, those who developed diabetic ketosis or ketoacidosis within 3 months of the onset of hyperglycemic symptoms were classified as having acute-onset T1D. In cases where the presence of ketosis could not be confirmed from medical records, acute-onset T1D was defined based on a fasting serum C-peptide level <0.6 ng/mL within 1 year of the T1D diagnosis.

In accordance with the 2023 diagnostic criteria revision for SPIDDM, a fasting serum C-peptide level of <0.6 ng/mL at the final observation point was categorized as "definite SPIDDM," whereas levels above that were categorized as "probable SPIDDM."[8,9] In December 2023, we examined the medical records and diagnosed definite or probable SPIDDM.

### Statistical analysis

Statistical analysis was conducted using JMP®17 (SAS Institute Inc., Cary, NC, USA). Continuous data are expressed as the arithmetic mean ± SD or median (25%–75%). Categorical data are expressed as the actual frequencies and percentages. The $t$-test was used for continuous data with a normal distribution, while the Wilcoxon test was used for data with a nonnormal distribution. The $\chi^2$ test was performed for the comparison of categorical variables. $p < 0.05$ were considered significant.

## RESULTS

### Distribution of the three subtypes of T1D

After the inclusion and exclusion criteria were applied, data of 482 Japanese individuals with T1D (161 men and 321 women) were analyzed. Among all patients, 62% ($n$ = 299) had acute-onset T1D, 27% ($n$ = 131) had SPIDDM, and 11% ($n$ = 52) had fulminant T1D. Table 1 presents the frequency of each subtype for every 10-year age group. The number of individuals in all subtypes decreased with increasing age at onset. In particular, the number of individuals with acute-onset T1D

**Table 1** | Baseline characteristics of adult-onset type 1 diabetes

| Age of diagnosis (years) | 20–29 ($n$ = 185) | 30–39 ($n$ = 146) | 40–49 ($n$ = 68) | 50–59 ($n$ = 43) | 60–69 ($n$ = 25) | 70–79 ($n$ = 15) |
|---|---|---|---|---|---|---|
| Subtype Ful/Acute/SP ($n$) (%) | 12/144/29<br>6/78/16 | 17/93/36<br>11/64/25 | 11/33/24<br>16/49/35 | 6/17/20<br>14/40/46 | 4/8/13<br>16/32/52 | 2/4/9<br>13/27/60 |
| Female (%) | 69 | 67 | 50 | 65 | 80 | 80 |
| BMI at onset (kg/m$^2$) | 20.4 (±2.9)<br>($n$ = 180) | 20.0 (±3.3)<br>($n$ = 128) | 20.5 (±3.1)<br>($n$ = 58) | 20.6 (±3.0)<br>($n$ = 40) | 20.2 (±2.6)<br>($n$ = 21) | 20.5 (±1.8)<br>($n$ = 15) |
| HbA1c at onset (%) | 11.0 [8.3–13.2]<br>($n$ = 175) | 10.4 [8.1–12.4]<br>($n$ = 125) | 9.4 [7.0–12.8]<br>($n$ = 59) | 10.0 [7.7–12.2]<br>($n$ = 37) | 9.8 [8.2–12.2]<br>($n$ = 21) | 8.6 [6.9–11.3]<br>($n$ = 11) |

Mean ± SD, median [quantile]. Acute, acute-onset type 1 diabetes; Ful, fulminant type 1 diabetes; SP, slowly progressive type 1 diabetes.

markedly decreased from the age of 30 ($n$ = 93) to 40 years ($n$ = 33). The proportion of fulminant T1D remained relatively constant across age groups, whereas the percentage of acute-onset T1D decreased from 78% in the 20–29 age group to 27% in the 70–79 age group. Conversely, the proportion of SPIDDM significantly increased with age, ranging from 16% in the 20–29 age group to 60% in the 70–79 age group.

### Clinical features of each subtype by age at onset

To elucidate the clinical characteristics based on age at onset, we determined the median age of onset for each subtype of T1D and used it as the cutoff value to compare clinical data between the early-onset and late-onset groups. The median age of onset was 37 years for fulminant T1D, 31 years for acute-onset T1D, and 40 years for SPIDDM.

As shown in Table 2, among individuals with fulminant T1D, the early-onset group exhibited a higher prevalence of GADAb positivity than the late-onset group. Seven of 52 individuals (13%) with fulminant T1D were GADAb-positive, with titers ranging from 1.6 to 7.1 U/mL. There were no significant differences in sex, BMI, HbA1c, fasting C-peptide levels, or daily insulin dosage at onset.

Among individuals with acute-onset T1D, blood glucose levels at onset were significantly higher in the early-onset group

**Table 2** | Comparison of clinical characteristics divided by onset age in three subtypes of type 1 diabetes

| Age of diagnosis (years) | Fulminant | | | | | Acute | | | | | SPIDDM | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $n$ | 20–36 ($n$ = 25) | $n$ | ≧37 ($n$ = 27) | $P$† | $n$ | 20–30 ($n$ = 151) | $n$ | ≧31 ($n$ = 148) | $P$† | $n$ | 20–39 ($n$ = 65) | $n$ | ≧40 ($n$ = 66) | $P$† |
| Male/Female ($n$) | 25 | 5/20 | 27 | 11/16 | 0.14 | 151 | 45/106 | 148 | 52/96 | 0.39 | 65 | 24/41 | 66 | 24/42 | 0.93 |
| BMI at onset (kg/m$^2$) | 22 | 21.1 (±2.8) | 22 | 20.8 (±2.5) | 0.56 | 146 | 20.1 (±2.6) | 136 | 19.9 (±3.2) | 0.20 | 58 | 21.0 (±3.7) | 58 | 20.7 (±2.9) | 0.91 |
| HbA1c at onset (%) | 23 | 6.3 [5.8–6.7] | 20 | 6.5 [6.1–6.9] | 0.40 | 143 | 11.6 [9.9–13.6] | 137 | 11.1 [9.1–12.7] | 0.053 | 54 | 8.8 [6.7–11.9] | 50 | 9.4 [7.0–12.9] | 0.21 |
| Blood glucose at onset (mg/dL) | 23 | 600 [546–743] | 27 | 661 [500–827] | 0.48 | 169 | 446 [322–556] | 109 | 396 [284–526] | 0.01* | 40 | 209 [146–363] | 43 | 304 [177–468] | 0.09 |
| Fasting C-peptide (ng/mL) | 16 | 0.2 [0.1–0.2] | 20 | 0.2 [0.04–0.2] | 0.19 | 119 | 0.4 [0.2–0.7] | 105 | 0.3 [0.2–0.5] | 0.13 | 35 | 1.0 [0.6–1.6] | 25 | 0.9 [0.4–1.4] | 0.20 |
| GAD Ab positive | 25 | 24% | 27 | 4% | 0.04* | 151 | 81% | 148 | 78% | 0.47 | 64 | 95% | 66 | 92% | 0.72 |
| GAD Ab (RIA) (U/mL) | | – | | – | – | 147 | 8.4 [3.7–44] | 146 | 7.0 [3.7–44] | 0.98 | 64 | 34.4 [6.9–150] | 66 | 42.4 [6.0–121] | 0.99 |
| Period between diagnosis and initiation of insulin (years) | | – | | – | – | | – | | – | – | 64 | 0.66 [0.08–1.7] | 65 | 0.44 [0.03–1.7] | 0.61 |
| Definite SPIDDM ($n$ = 101) | | | | | | | | | | | 51 | 88% | 50 | 90% | 0.58 |
| Daily insulin dosage (U/kg) | 15 | 0.67 (±0.17) | 24 | 0.66 (±0.20) | 1.00 | 124 | 0.57 (±0.28) | 127 | 0.52 (±0.23) | 0.09 | | | | | |

Mean ± (SD), median [quantile]. The values for fasting C-peptide and GAD antibodies (GADAb) were recorded within 1 year of diagnosis for fulminant type 1 diabetes and acute-onset type 1 diabetes, and at the time when GADAb positivity was first confirmed for SPIDDM. Acute, acute-onset type 1 diabetes; Fulminant, fulminant type 1 diabetes; SPIDDM, slowly progressive type 1 diabetes. * Represent p<0.05. †Early-onset versus late-onset groups.

than in the late-onset group. However, there were no significant differences in sex, BMI, HbA1c, fasting C-peptide levels, GADAb positivity, GADAb titers, or daily insulin dosage between the early-onset and late-onset groups.

Among individuals with SPIDDM, there were no significant differences in sex, BMI, HbA1c, blood glucose, fasting C-peptide levels, GADAb positivity and titers, or the period between diabetes diagnosis and initiation of insulin therapy, between the early-onset and late-onset groups.

We were able to distinguish between definite and probable SPIDDM in 104 of 131 individuals. In the early-onset group, 88% of individuals were classified as having "definite SPIDDM," whereas in the late-onset group, this percentage was 90%, with no significant difference. In other words, 12% of the early-onset group and 10% of the late-onset group were diagnosed with probable SPIDDM.

### Comparison between definite and probable SPIDDM

Table 3 shows the comparison between definite and probable SPIDDM. In 2023, the duration of T1D was 16 years in both groups. In definite SPIDDM, BMI and fasting C-peptide values were significant lower at diagnosis. No significant differences were observed in age at onset, sex, HbA1c, blood glucose levels, positivity rate and titers of GAD antibodies, and the duration from diagnosis to initiation of insulin therapy. Figure 1 shows the proportions of definite SPIDDM and probable SPIDDM

**Table 3** | Comparison of clinical characteristics between definite SPIDDM and probable SPIDDM

| | Definite SPIDDM | | Probable SPIDDM | | *P* value |
|---|---|---|---|---|---|
| | *n* | 89 | *n* | 12 | |
| Age of diagnosis (years) | 89 | 42 ± 15 | 12 | 41 ± 13 | 0.78 |
| Duration of diabetes* (years) | 89 | 16 ± 4 | 12 | 16 ± 4 | 0.59 |
| Male/Female (*n*) | 89 | 32/57 | 12 | 7/5 | 0.21 |
| BMI at onset (kg/m$^2$) | 79 | 20.8 ± 3.4 | 11 | 22.7 ± 3.0 | **0.04** |
| HbA1c at onset (%) | 67 | 8.4 [6.8–11.9] | 10 | 10.7 [8.4–12.9] | 0.22 |
| Blood glucose at onset (mg/dL) | 55 | 223 [140–430] | 7 | 244 [200–468] | 0.63 |
| Fasting C-peptide (ng/mL) | 41 | 0.8 [0.4–1.2] | 6 | 1.9 [1.4–2.0] | **0.01** |
| GAD Ab positive (%) | 89 | 93 | 12 | 92 | 1.00 |
| GAD Ab (RIA) (U/mL) | 88 | 25.3 [6.3–111.3] | 12 | 18.4 [3.0–43.2] | 0.28 |
| Period between diagnosis and initiation of insulin (years) | 89 | 0.6 [0.1–1.4] | 12 | 0.1 [0.0–2.2] | 0.70 |

Duration of diabetes* means the duration at the year of 2024. SPIDDM: Slowly progressive type 1 diabetes Mean ± standard deviation, median [quantile].

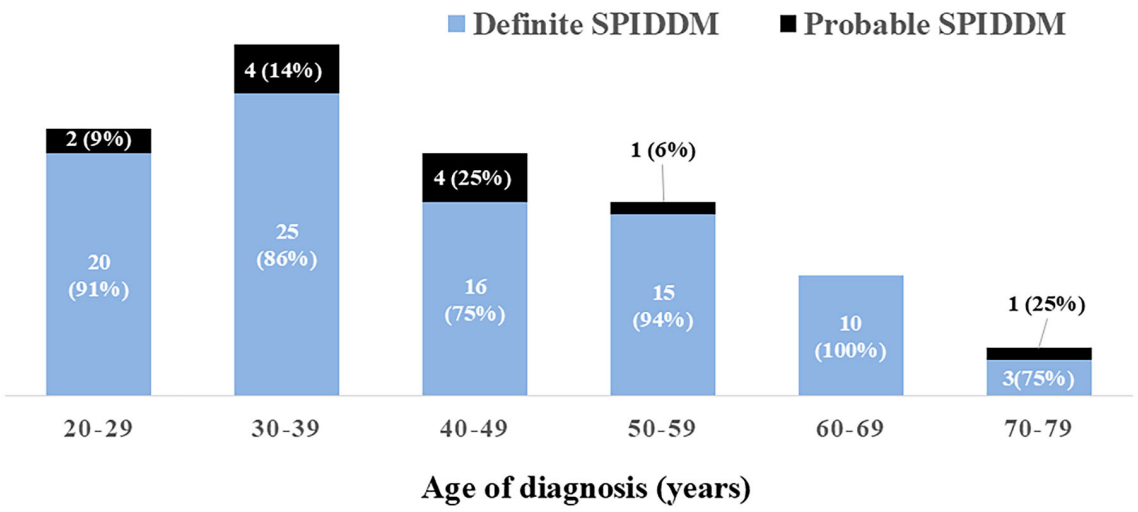


**Figure 1** | Proportion of definite and probable SPIDDM by age of diagnosis >20 years old. The proportion of definite and probable SPIDDM was almost equal in all age groups.

based on the age of onset of SPIDDM in 10-year intervals. No significant differences were observed across the different age groups.

### Missing data

Among the 482 participants, 297 (62%) had their first visit within 1 year of diagnosis, and their examination data were obtained from our hospital or a referral letter. For those who had visited our hospital after the first year of diagnosis, the examination data were referenced from letters received from other hospitals, leading to some missing data. Tables 2 and 3 present the number of participants for each test item. A comparison between participants who visited within the first year of diagnosis and participants who did not reveal any significant differences in age, subtype, and sex (data not shown). Despite the occurrence of missing data, diabetes specialists carefully diagnosed the subtype of type1 diabetes based on the initial patient interviews and the information provided in referral letters from previous physicians, adhering to the guidelines.

The missing data were as follows. For acute-onset T1D, data for blood glucose levels were missing for 21 individuals, HbA1c values for 19 individuals, and BMI were missing for 17 individuals. Additionally, fasting C-peptide levels within the first year of onset were unavailable for 75 patients, and insulin usage data were unattainable for 48 individuals. Similarly, for fulminant T1D, missing data were observed for blood glucose levels in 2 patients, HbA1c values in 9, 8 for BMI data, 16 for information on fasting C-peptide values, and 13 for insulin usage data. Even when these data were missing, the case was classified as fulminant T1D if a referral letter from a diabetes specialist at another institution indicated such a diagnosis. In these cases, the referral letter often included descriptions such as "endogenous insulin secretion is depleted," "meets the diagnostic criteria for fulminant type 1 diabetes," or provided values such as random C-peptide levels or urinary C-peptide levels. In individuals with SPIDDM for whom insulin therapy was not initiated at the first visit, endogenous insulin secretion was evaluated using serum insulin levels instead of C-peptide; as a result, there were many instances of missing data. Since there was no ketosis or ketoacidosis at the time of diagnosis and insulin therapy was initiated more than 3 months after diagnosis, these cases were classified as SPIDDM. The missing data included blood glucose levels for 48 patients, HbA1c values for 27 patients, BMI values for 15 patients, fasting C-peptide values for 71 patients, and period between diagnosis and initiation of insulin for two patients.

## DISCUSSION

This hospital-based study demonstrated that the number of adults with newly-onset T1D visiting our hospital decreased with age. Further, the proportion of subtypes of adult-onset T1D varied with age at onset (the proportion of fulminant T1D was approximately equivalent throughout all age groups; however, the proportion of acute-onset T1D significantly decreased with age, and the proportion of SPIDDM significantly increased with age). Among individuals with fulminant T1D, those who were GADAb-positive were younger at onset than those who were GADAb-negative. Finally, in definite SPIDDM, the BMI and fasting C-peptide levels at diagnosis were significantly lower compared with those of probable SPIDDM.

### Proportion of subtypes in adult-onset T1D

Among patients with adult-onset T1D, 62% had acute-onset T1D, 27% had SPIDDM, and 11% had fulminant T1D. Murao *et al.* reported that in the Ehime Study, 113 patients were diagnosed with T1D, with approximate proportions of 50% for acute-onset T1D, 17% for intermediate onset (insulin treatment was initiated between 3 and 12 months after onset), 9% for fulminant T1D, and 24% for slowly progressive T1D; the patients' age at onset was significantly younger for acute-onset T1D than for SPIDDM (39 ± 15 vs 47 ± 14 years)[14]. The present study confirms that the proportion of subtypes varies according to the age at onset; therefore, variation in the proportion of subtypes in previous studies was probably due to participant selection based on the age at onset.

Regarding the proportion of fulminant T1D in Japan, a nationwide multicenter study indicated that 19.4% of cases with adult-onset T1D with ketosis onset at disease onset were fulminant T1D[10]. In a multicenter survey conducted in Korea, 14.6% of all patients with T1D with ketosis onset were diagnosed with fulminant T1D[15]. The proportion of fulminant T1D among ketosis-onset (acute-onset and fulminant T1D) cases was 15% in the present study, consistent with the results of the Japanese and Korean multicenter studies.

### Characteristics of T1D subtype by age at onset

#### *Fulminant T1D*

In our study, the proportion of fulminant T1D was equivalent throughout all age groups. A nationwide survey of pediatric-onset T1D in Japan revealed a remarkably low proportion, with only 16 of 1,076 individuals diagnosed (1.5%)[16]. Siga *et al.* reported that pediatric-onset fulminant T1D is considered rare because pediatricians are not familiar with it; hence, some cases of fulminant T1D may not be identified. Furthermore, in pediatric-onset fulminant T1D, three of 15 individuals (20%) were GADAb-positive[16]. In our study, 13% of individuals were GADAb-positive, with a significantly higher positivity rate observed in the early-onset group. In comparison, previous studies have reported GADAb positivity rates of 5%–9% among adults with fulminant T1D, which is lower than our findings. Further investigation is needed to understand the age-related differences in GADAb positivity rates among individuals diagnosed with fulminant T1D.

#### *SPIDDM*

In the analysis of SPIDDM, we observed no significant difference in the duration from diagnosis to the initiation of insulin

therapy between the early-onset and late-onset groups. Additionally, based on the C-peptide values assessed in 2023, we observed that 89% of individuals with SPIDDM (88% of individuals in the early-onset group and 90% in the late-onset group) met the criteria for definite SPIDDM.

In this study, BMI and C-peptide levels among individuals with probable SPIDDM were significantly higher than those among individuals with definite SPIDDM. On the contrary, no significant differences were observed in GADAb levels and the age of diabetes diagnosis between both groups. Previously, we reported that the period from diabetes diagnosis to the initiation of insulin treatment was significantly shorter in the group with a BMI of less than 22 kg/m$^2$ at diagnosis. Additionally, regardless of the presence of obesity, all individuals with SPIDDM had a C-peptide index of 1.0 or lower at the time of SPIDDM diagnosis[17]. Wada *et al.* found that in individuals with SPIDDM, higher BMI (≥22 kg/m$^2$), lower HbA1c (<75 mmol/mol [9.0%]), and lower GADAb levels (<10.0 U/mL) at the initial identification of positive GAD antibodies were predictors of a non-insulin-dependent state in the future[18]. Additionally, Yasui *et al.* reported that in Japanese patients with SPIDDM, those who did not require insulin therapy for >5 years had higher BMI, older age, higher fasting C-peptide levels, and lower GADAb levels (≥13.6 U/mL) at the time of GAD-positive diabetes compared to those requiring insulin therapy within 5 years[19]. These findings, along with the results of our study, suggest that definite SPIDDM is characterized by lower BMI and C-peptide levels, indicating a state closer to acute-onset T1D at the time of diagnosis. Further investigation is needed to identify the risk factors for definite SPIDDM. Other risk factors for progression from probable SPIDDM to insulin-dependent status include high GAD antibody levels, positivity for multiple islet-related autoantibodies[20–24], and positive thyroid peroxidase antibodies[14]. As this study was based on a real clinical setting, GADAb levels were measured only in cases with negative GADAb because measuring multiple islet-related autoantibodies was not possible.

Age differences in the progression of SPIDDM to insulin-dependent status have been noted in several studies[14], emphasizing a higher progression rate in younger patients. Yasui *et al.* reported that the optimal cutoff value for progressing to an insulin-requiring status was 47 years[19]. In these studies, insulin dependency was investigated 3–5 years after diagnosis. In our study, we evaluated whether it was probable or definite SPIDDM over an average duration of 16 years. The C-peptide level may gradually decrease with prolonged observation, and differences based on age or GADAb levels may become less apparent.

### Strengths and limitations

This study has some limitations. First, it was a single-center study, and institution-specific factors may limit the generalizability of the results. Most participants lived in Tokyo and its neighboring prefectures, potentially introducing regional variations into the data. Second, because our facility operates within an urban university hospital, some of the study participants visited the facility for advanced fertility treatment options, potentially leading to a higher proportion of women in their 20s and 30s compared with the typical Japanese population with T1D. Third, the data used in this study were extracted from medical records using the term "Type 1 diabetes," which prevented the inclusion of those with T1D described solely as "diabetes." Fourth, as the investigation was based on past medical records, some detailed data were missing. Moreover, our study may have inadequately detected cases of SPIDDM, as we did not measure GADAb and other islet-associated autoantibodies unless SPIDDM was clinically suggested.

Nonetheless, our research possesses several notable strengths. We conducted a comprehensive study encompassing all patients who visited a single hospital for 13 years, identifying 482 individuals with newly diagnosed adult-onset T1D. In Japan, there is no central database for individuals with adult-onset T1D. Therefore, it is difficult to determine the real-world age distribution of the disease. Furthermore, in a previous study, the definition of adult-onset T1D included individuals ≥20 years without considering the differences between individuals in their 20s and those in their 70s. This study divided the adult population into 10-year segments and examined the proportion of the subtypes within each group. Additionally, in 2023, the diagnostic criteria for SPIDDM were newly revised by the Japan Diabetes Society. As this study was conducted at a single facility, some patients have been continuously followed since the initial survey. A strength of this study is that in 2023, we were able to evaluate C-peptide levels and confirm definite SPIDDM and probable SPIDDM in the target patients.

Our study revealed that as the onset age increased, the number of individuals with acute-onset T1D decreased, and the proportion of those with SPIDDM increased. The proportion of fulminant T1D was nearly constant. Definite SPIDDM had significantly lower fasting C-peptide levels and BMI at the time of diabetes diagnosis compared to probable SPIDDM. Our findings suggest that the heterogeneity of adult-onset T1D may be related to the age at onset; thus, further research is required to corroborate our findings.

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## DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This study conformed to the standards of the Declaration of Helsinki. Ethics Committee of Tokyo Women's Medical University.

Informed Consent: N/A.

Approval date of Registry and the Registration No. of the study/trial: April 16, 2018. No. 4756.
Animal Studies: N/A.

## REFERENCES

1. Thomas NJ, Jones SE, Weedon MN, *et al*. Frequency and phenotype of type 1 diabetes in the first six decades of life: A cross-sectional, genetically stratified survival analysis from UK biobank. *Lancet Diabetes Endocrinol* 2018; 6: 122–129.
2. Takeda H, Kawasaki E, Shimizu I, *et al*. Clinical, autoimmune, and genetic characteristics of adult-onset diabetic patients with GAD autoantibodies in Japan (Ehime study). *Diabetes Care* 2002; 25: 995–1001.
3. Tanaka S, Awata T, Shimada A, *et al*. Clinical characteristics of slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM): 1st subcommittee report on SPIDDM, committee on type 1 diabetes, Japan diabetes society. *J Japan Diab Soc* 2011; 54: 65–75 (Japanese).
4. Tsuruoka A, Matseba I, Toyota T, *et al*. Antibodies to GAD in Japanese diabetic patients: A multicenter study. *Diabetes Res Clin Pract* 1995; 28: 191–199.
5. Hamaguchi K, Kimura A, Kusuda Y, *et al*. Clinical and genetic characteristics of GAD-antibody positive patients initially diagnosed as having type 2 diabetes. *Diabetes Res Clin Pract* 2004; 66: 163–171.
6. Kawasaki E, Matsuura N, Eguchi K. Type 1 diabetes in Japan. *Diabetologia* 2006; 49: 828–836.
7. Kawasaki E, Eguchi K. Current aspects on the clinical immunology and genetics of autoimmune diabetes in Japan. *Diabetes Res Clin Pract* 2007; 77(Suppl 1): S104–S109.
8. Shimada A, Kawasaki E, Abiru N, *et al*. New diagnostic criteria (2023) for slowly progressive type 1 diabetes (SPIDDM): Report from committee on type 1 diabetes in Japan diabetes society. *Diabetol Int* 2024; 15: 1–4.
9. Shimada A, Kawasaki E, Abiru N, *et al*. New diagnostic criteria (2023) of slowly progressive type 1 diabetes (SPIDDM) -report from committee of type 1 diabetes in Japan diabetes society. *J Japan Diab Soc* 2023 66: 807–814.
10. Imagawa A, Hanafusa T, Uchigata Y, *et al*. Fulminant type 1 diabetes: A nationwide survey in Japan. *Diabetes Care* 2003; 26: 2345–2352.
11. Imagawa A, Hanafusa T, Awata T, *et al*. Report of the Committee of the Japan Diabetes Society on the research of fulminant and acute-onset type 1 diabetes mellitus: New diagnostic criteria of fulminant type 1 diabetes mellitus (2012). *J Diabetes Investig* 2012; 3: 536–539.
12. Kawasaki E, Maruyama T, Imagawa A, *et al*. Diagnostic criteria for acute-onset type 1 diabetes mellitus (2012). Report of the Committee of Japan Diabetes Society on the research of fulminant and acute-onset type 1 diabetes mellitus. *Diabetol Int* 2013; 4: 221–225.
13. Tanaka S, Ohmori M, Awata T, *et al*. Diagnostic criteria for slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM) (2012): Report by the committee on slowly progressive insulin-dependent (type 1) diabetes mellitus of the Japan Diabetes Society. *Diabetol Int* 2015; 6: 1–7.
14. Murao S, Makino H, Kaino Y, *et al*. Differences in the contribution of HLA-DR and -DQ haplotypes to susceptibility to adult- and childhood-onset type 1 diabetes in Japanese patients. *Diabetes* 2004; 53: 2684–2690.
15. Song SO, Yun JS, Ko SH, *et al*. Prevalence and clinical characteristics of fulminant type 1 diabetes mellitus in Korean adults: A multi-institutional joint research. *J Diabetes Investig* 2022; 13: 47–53.
16. Shiga K, Urakami T, Suzuki J, *et al*. Fulminant type 1 diabetes mellitus in Japanese children and adolescents: Multi-institutional joint research of the Japanese study Group of Insulin Therapy for childhood and adolescent diabetes. *Endocr J* 2018; 65: 795–803.
17. Hoshina S, Miura J, Sugisawa E, *et al*. Clinical features of slowly progressive type 1(insulin -dependent) diabetes mellitus: A comparative study based on degree of obesity at diagnosis of diabetes. *Diabetol Int* 2015; 6: 91–97.
18. Wada E, Onoue T, Kinoshita T, *et al*. Adult-onset autoimmune diabetes identified by glutamic acid decarboxylase autoantibodies: A retrospective cohort study. *Diabetologia* 2021; 64: 2183–2192.
19. Yasui J, Kawasaki E, Tanaka S, *et al*. Clinical and genetic characteristics of non-insulin-requiring glutamic acid decarboxylase (GAD) autoantibody-positive diabetes: A nationwide survey in Japan. *PLoS One* 2016; 11: e0155643.
20. Kawasaki E, Nakamura K, Kuriya G, *et al*. Autoantibodies to insulin, insulinoma-associated antigen-2, and zinc transporter 8 improve the prediction of early insulin requirement in adult-onset autoimmune diabetes. *J Clin Endocrinol Metab* 2010; 95: 707–713.
21. Maruyama T, Tanaka S, Shimada A, *et al*. Insulin intervention in slowly progressive insulin-dependent (type 1) diabetes mellitus. *J Clin Endocrinol Metab* 2008; 93: 2115–2121.
22. Kawasaki E. Anti-islet autoantibodies in type 1 diabetes. *Int J Mol Sci* 2023; 24: 10012.
23. Tanaka S, Okubo M, Nagasawa K, *et al*. Predictive value of titer of GAD antibodies for further progression of beta cell dysfunction in slowly progressive insulin-dependent (type 1) diabetes (SPIDDM). *Diabetol Int* 2015; 7: 42–52.
24. Turner R, Stratton I, Horton V, *et al*. UKPDS 25: Autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *Lancet* 1997; 350: 1288–1293.