

Slowly progressive subtype of childhood-onset type 1 diabetes as a high-risk factor for end-stage renal disease: A cohort study in Japan

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ABSTRACT

Aim: To compare the incidence of end-stage renal disease (ESRD) between slowly progressive type 1 diabetes and acute-onset type 1 diabetes.

Methods: This cohort study enrolled all 521 patients with childhood-onset type 1 diabetes with the year of onset from 1959 to 1996 in Hokkaido Prefecture, Japan. We calculated the ESRD incidence rate per 100,000 person-years by sex, onset year, onset age, and type 1 diabetes subtype (slowly progressive or acute-onset). We also constructed a Kaplan–Meier curve for ESRD by these risk factors.

Results: The data of 391 patients were gathered, among whom 66 developed ESRD. The ESRD incidence rate per 100,000 person-years was 525 among all patients; 538 and 503 among women ($n = 235$) and men ($n = 156$); 893, 413, and 225 for onset year of 1959–1979 ($n = 107$), 1980–1989 ($n = 201$), and 1990–1996 ($n = 83$); 420 and 715 for onset before ($n = 243$) and after ($n = 148$) puberty; and 1388 and 432 for the slowly progressive ($n = 41$) and acute-onset ($n = 350$) subtypes, respectively. The Kaplan–Meier curve also indicated a significantly higher incidence of ESRD in slowly progressive than in acute-onset type 1 diabetes.

Conclusion: The incidence of ESRD was higher in slowly progressive than acute-onset type 1 diabetes.

1. Introduction

End-stage renal disease (ESRD) is a globally prevalent complication of diabetes¹ that restricts patients' quality of life and activities of daily living.² Although the incidence of ESRD in type 1 diabetes varies among nations,³ this incidence has decreased globally with recent improvements in diabetes care, including stricter control of plasma glucose, blood pressure, and serum lipid levels.^{4–9} Type 1 diabetes can be diagnosed at any age¹⁰ and is divided into subtypes,¹¹ but data on the incidence of ESRD by subtype are scarce. Investigating the risk factors could aid in risk stratification, which is essential to promote individualised ESRD prevention and treatment strategies.

Several risk factors for microvascular complications in patients with type 1 diabetes have been presented in previous studies, including a high

glycated haemoglobin concentration,¹² variability in the glucose concentration,^{13,14} onset during puberty,¹⁵ and possibly high glycosylation rates. These risk factors may vary among individuals with different genetic dispositions. Cohort studies of Asian patients could add evidence regarding these risk factors.

Among the subtypes of type 1 diabetes, slowly progressive type 1 diabetes (historically termed slowly progressive insulin-dependent diabetes mellitus [SPIDDM])¹⁶ is characterised by progressive beta-cell failure. Initially, patients do not require insulin therapy; however, they ultimately become dependent on insulin therapy over several years. Evidence on the incidence of microvascular disease in slowly progressive type 1 diabetes compared with acute-onset type 1 diabetes is scarce. It is generally considered that among individuals with onset of type 1 diabetes or type 2 diabetes during young adulthood, type 1 diabetes has

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a more favourable prognosis, largely because of earlier therapeutic intervention.¹⁷ Considering that the incidence of diabetic nephropathy in patients with latent autoimmune diabetes mellitus (LADA), also known as slowly progressive type 1 diabetes that develops in adulthood,^{18,19} may be similar to or higher than that in patients with type 2 diabetes, we hypothesised that the incidence of ESRD in patients with slowly progressive type 1 diabetes may be higher than that in patients with acute-onset type 1 diabetes. In this study, we compared the incidence of ESRD between slowly progressive and acute-onset type 1 diabetes in a cohort of patients with childhood-onset type 1 diabetes.

2. Methods

2.1. Enrolment

The setting of this cohort study was Hokkaido Prefecture, which is composed of the northernmost islands of Japan. From 1959 to 1996, the Childhood IDDM Hokkaido Registry²⁰ enrolled all children who developed insulin-dependent diabetes mellitus at the age of <15 years in Hokkaido Prefecture. The baseline time point of this study was 1959 to 1996, when the patients developed the disease. Because islet cell antibodies were not usually measured in patients with insulin-dependent diabetes mellitus (IDDM) from 1959 to 1996, detecting type 1 diabetes according to the contemporary definition among these patients was difficult. Therefore, we considered these patients with IDDM to have type 1 diabetes.²¹ From January 2020 to March 2022, we requested information about the patients in the registry from the attending physicians by postal mail and/or telephone call for this cohort study. The physicians who cooperated with the survey completed the questionnaire by transcribing the patients' information from the medical records.

2.2. Exposure and outcome variables

Sex, birth date, date of diagnosis, and age at diagnosis of type 1 diabetes were obtained from the registry as mentioned above.²⁰ In this study, we reviewed the records in the registry to obtain the baseline exposures. The primary endpoint was the introduction of dialysis (including haemofiltration and peritoneal dialysis) or renal transplantation for ESRD. We also recorded death in the cohort. Patients who were lost to follow-up or died before developing ESRD were censored.

Acute-onset type 1 diabetes was clinically defined as the development of polydipsia, polyuria, weight loss, or fatigue; the presence of hyperglycaemia; the presence of ketosis or ketonuria; and the need for insulin treatment within 3 months from diagnosis of diabetes. Because fulminant type 1 diabetes was reported and established in the year 2000,²² which was after the baseline of this study, fulminant type 1 diabetes was not medically defined at the baseline. Therefore, the fulminant-onset subtype is considered to have been included in the acute-onset type in this study. Slowly progressive type 1 diabetes was clinically defined as the incidental detection of hyperglycaemia, such as through positive urine glucose found in a school urinalysis; the requirement for insulin treatment beginning 3 to 12 months after the diagnosis of type 1 diabetes; few symptoms of polydipsia and polyuria; no ketosis or ketonuria at the start of treatment; and percentage of overweight of <30 %.²³ The diagnostic criteria for slowly progressive type 1 diabetes, including positive islet-associated autoantibody at some point during the disease course, were newly released by the Japan Diabetes Society in 2023.^{16,24} Because the antibody test could not be used in the baseline period of our cohort, we did not adopt the criterion of positive islet-associated autoantibody. Instead, four paediatricians specialising in diabetes among the present authors reviewed the baseline records at the time of diagnosis and identified cases of acute or slowly progressive type 1 diabetes by consensus.

2.3. Strata

We divided the patients into two groups by sex and age at onset (before and after puberty). 'After puberty' was defined as an age of ≥12 years for boys and ≥11 years for girls. Type 1 diabetes was grouped into the acute-onset subtype or slowly progressive subtype. To explore which characteristics had the highest ESRD rate, we constructed the following combinations of stratifications: sex and onset age, sex and onset subtype, and onset age and onset subtype.

2.4. Statistical analysis

The patients' characteristics are presented as number (percentage) or mean (standard deviation). We calculated the ESRD incidence rate per 100,000 person-years by strata of sex, onset year, onset age, and onset type. We constructed a Kaplan–Meier curve²⁵ from the diagnosis of type 1 diabetes to the outcome of ESRD by strata of sex, onset age, onset type, and their combinations. We also constructed a curve from initiation of dialysis or performance of renal transplantation to death by strata of sex, onset age, and onset subtype.

We used the log-rank test²⁶ to assess the significance of the differences between survival curves. The statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA). R statistical software version 4.2.2 (R Project for Statistical Computing, Vienna, Austria) was used to generate Kaplan–Meier estimates. All reported *p* values were two-sided, and *p* < 0.05 indicated a significant difference.

3. Results

Of 521 patients who developed type 1 diabetes at the age of <15 years in Hokkaido Prefecture from 1959 to 1996, 391 responded to the survey and were included in the cohort study (response rate: 75 %). Overall, 66 patients developed ESRD. Table 1 shows the patient characteristics at baseline and the ESRD incidence rate per 100,000 person-years. The median follow-up duration for ESRD was 33.1 (interquartile range: 27.8–38.2) years. The mean age at onset among the 391 patients was 8.9 (standard deviation: 3.7) years, and 235 (60.1 %) patients were female. One hundred seven (27.4 %) patients developed type 1 diabetes from 1959 to 1979, 201 (51.4 %) from 1980 to 1989, and 83 (21.2 %) from 1990 to 1996. Two hundred forty-three (62.1 %) patients developed type 1 diabetes before puberty, and 41 (10.5 %) had the slowly progressive subtype.

Fig. 1A to C shows the time from onset of type 1 diabetes to the development of ESRD according to sex, before or after puberty, and acute onset or slowly progressive type of type 1 diabetes. There was no significant difference in the development of ESRD between the two sexes. Patients with onset after puberty had a higher incidence of ESRD

Table 1

Characteristics of patients with onset of type 1 diabetes from 1959 to 1996 and their ESRD incidence rate.

Characteristics	Value	ESRD incidence rate [†]
Overall	391	525 (385–633)
Age at onset, years	8.9 ± 3.7	–
Women	235 (60.1)	538 (367–687)
Men	156 (39.9)	503 (307–713)
Onset between 1959 and 1979	107 (27.4)	893 (554–1117)
Onset between 1980 and 1989	201 (51.4)	413 (263–581)
Onset between 1990 and 1996	83 (21.2)	225 (72–517)
Onset before puberty	243 (62.1)	420 (280–565)
Onset after puberty	148 (37.9)	715 (450–929)
Acute-onset type	350 (89.5)	432 (306–546)
Slowly progressive type	41 (10.5)	1388 (706–1940)

Data are presented as mean ± standard deviation, n, or n (%).

[†]ESRD incidence rate per 100,000 person-years (95 % confidence interval). ESRD, end-stage renal disease.

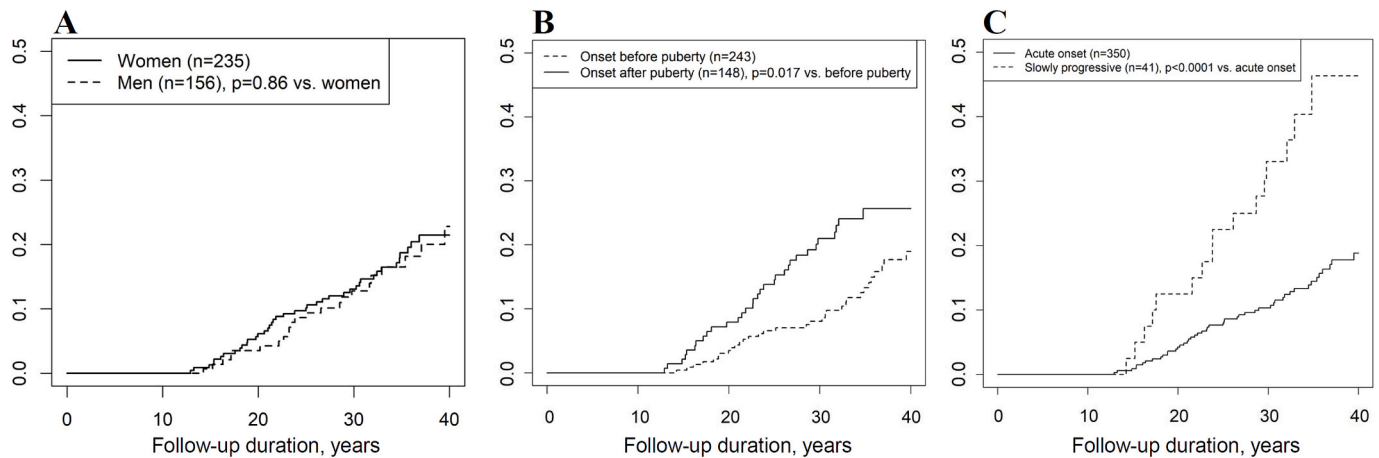


Fig. 1. Onset of end-stage renal disease in patients with type 1 diabetes according to sex, onset age, and subtype.

than those with onset before puberty. Notably, the incidence of ESRD was higher in patients with the slowly progressive subtype than acute-onset subtype of type 1 diabetes.

Fig. 2A to C shows the time from onset of type 1 diabetes to the development of ESRD according to combinations of sex, onset type, and onset type. Among the combinations of stratifications, male sex and the slowly progressive type were associated with the highest incidence of ESRD.

Fig. 3A to C shows the time from ESRD development to death in patients with type 1 diabetes. After the development of ESRD, mortality in women tended to be higher than that in men, although there was no statistically significant difference. There was no significant difference in mortality between patients with onset before and after puberty or between the slowly progressive and acute-onset subtypes.

4. Discussion

The incidence of ESRD in patients with type 1 diabetes did not differ between sexes. However, patients with onset after puberty had a higher incidence of ESRD than those with onset before puberty. Patients with slowly progressive type 1 diabetes were more likely to develop ESRD than those with acute-onset type 1 diabetes. The detailed analysis showed that male patients with the slowly progressive subtype had the highest incidence of ESRD.

The Fremantle Diabetes Study showed that the incidence rate of macroalbuminuria in patients with LADA was significantly lower than in patients who had type 2 diabetes with negative glutamic acid

decarboxylase (GAD) antibodies.²⁷ GAD antibody positivity has been recognised as a key indicator for the diagnosis of slowly progressive type 1 diabetes.¹⁶ In the United Kingdom Prospective Diabetes Study, however, patients with LADA had a higher incidence of microvascular disease than patients with type 2 diabetes²⁸ when observed for >20 years. Whether the incidence of microvascular complications in patients with LADA is lower or higher than in patients with type 2 diabetes is controversial.²⁹ Some studies have shown that the incidence of nephropathy is lower in patients with LADA than in those with type 2 diabetes,^{27,30} whereas others have shown that it is similar or higher.^{31,32} This inconsistency may be explained by the fact that type 2 diabetes is diagnosed after a longer duration of hyperglycaemia from the onset, which leads to more damage of blood vessels. Additionally, a lower incidence of nephropathy is observed in studies with shorter mean follow-up durations of ≤ 5 years.

Evidence of microvascular complications during follow-up of patients with slowly progressive type 1 diabetes or LADA versus patients with acute-onset type 1 diabetes is scarce.³³ The slowly progressive subtype is expected to be more accurately diagnosed in the future. Subtype-specific treatment interventions based on prognostic predictions will become increasingly important. We consider that the present study adds prognostic evidence, suggesting a higher incidence of ESRD in slowly progressive type 1 diabetes than in acute-onset type 1 diabetes.

The cause of the high incidence of ESRD in patients with slowly progressive type 1 diabetes is unknown. Patients with this type of diabetes have few subjective symptoms. Treatment is likely to be delayed,

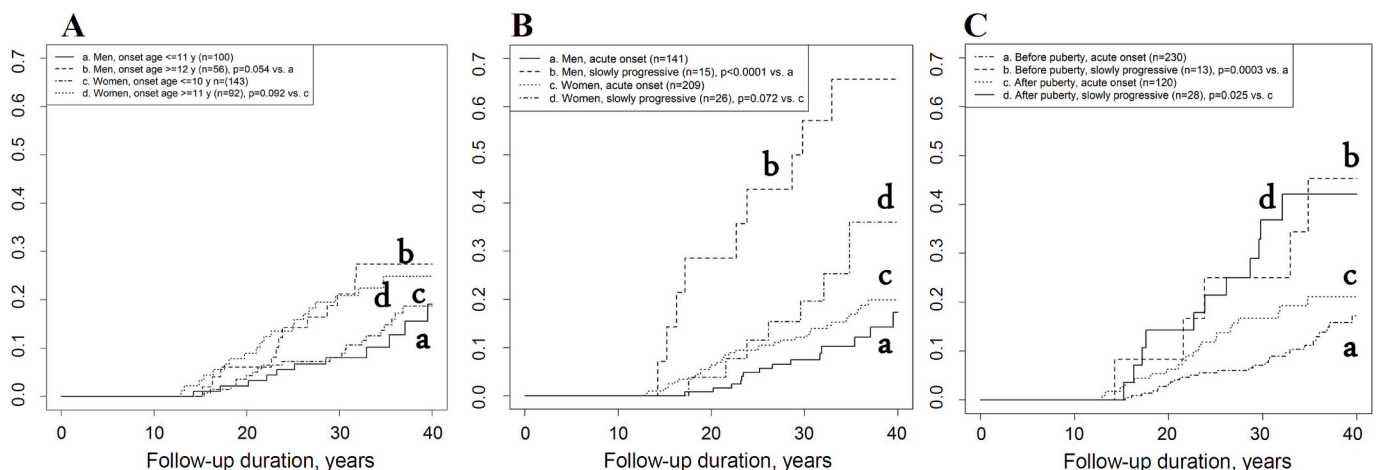


Fig. 2. Onset of end-stage renal disease in patients with type 1 diabetes according to combinations of sex, onset age, and subtype.

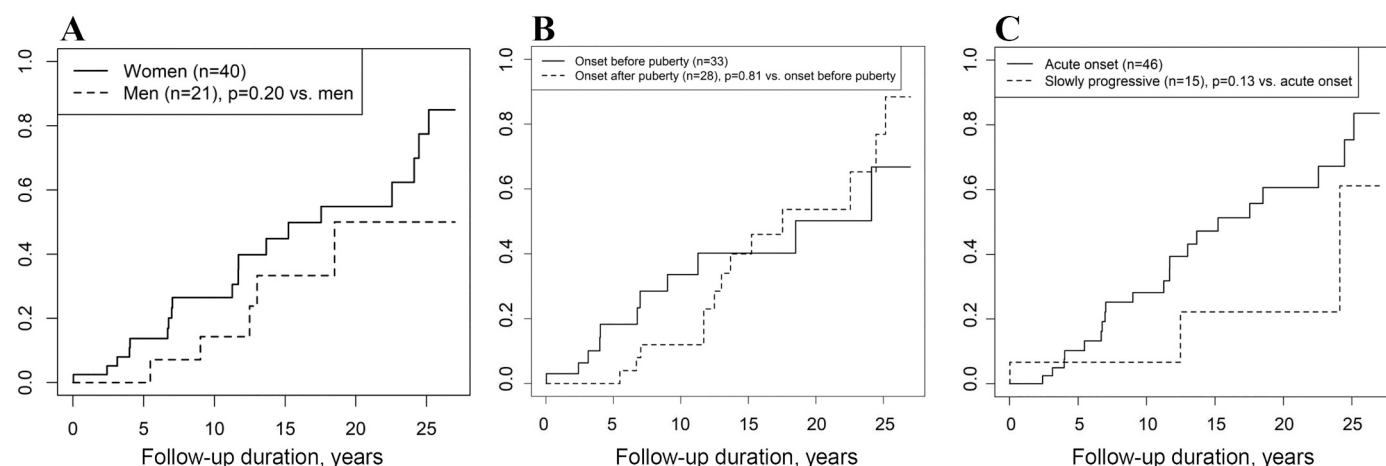


Fig. 3. Lifespan from diagnosis of end-stage renal disease in patients with type 1 diabetes according to sex, onset age, and subtype.

and patients are less willing to accept insulin therapy. As a result, blood glucose control is likely to be poor, blood vessels are likely to be damaged, and vascular complications may have developed by the time of diagnosis.

In the present study, male patients with the slowly progressive subtype had the highest incidence of ESRD (Fig. 2B). Previous reports indicating a male predominance in the slowly progressive subtype have suggested the potential influence of hormonal or immunological processes on β -cell failure.³⁴ A Finnish study revealed that among patients with an age at onset of ≥ 10 years, male sex is a risk factor for ESRD in type 1 diabetes.³⁵ Lower insulin secretion and sensitivity in men^{36,37} may affect the higher incidence of ESRD. Additionally, the higher prevalence of smoking and drinking habits in men than in women may explain this result. Furthermore, the mean age at marriage is higher in men than in women. Fewer opportunities to receive family and social support for male patients with the slowly progressive subtype may also contribute to the result. Moreover, a longer period of bachelorship means that the kidneys are more likely to be affected by high-salt food obtained outside the home.

Regarding the diagnostic criteria for the patients in this study, all patients had a relatively steep course of absolute insulin deficiency during baseline period and thus were considered to have developed type 1 diabetes. In 2023, the Japan Diabetes Society issued a new diagnostic criterion for slowly progressive type 1 diabetes.¹⁶ This criterion requires three conditions to be met for diagnosis of this subtype; one condition is a demonstration of pancreatic autoantibodies. However, no technology for the demonstration of anti-pancreatic body antibodies was available at the baseline of this study. By contrast, the diagnostic criteria for the slowly progressive subtype in this study are in line with the other two requirements.

In our analysis of the prognosis of ESRD (Fig. 3), we were unable to clearly identify the risk factors for shorter life expectancy. A meta-analysis revealed several risk factors for mortality in patients undergoing haemodialysis: advanced age, diabetes, cardiovascular disease history, high C-reactive protein, high glycated haemoglobin, high serum phosphate, and high brain natriuretic peptide.³⁸ Detailed analysis of data obtained from large-scale observational studies may further elucidate the risk factors for mortality in patients with type 1 diabetes and ESRD.

As indicated by the results of this study (Fig. 2B), clinicians need to prioritise interventions for male patients with slowly progressive type 1 diabetes because they are at the highest risk of developing ESRD. Additionally, because whether intensive care is the best intervention for patients with the slowly progressive subtype is unknown, studies on the most effective therapy for these patients are needed. In patients with the slowly progressive subtype, the insulin secretion capacity remains for a

longer period than in patients with the acute-onset subtype. The ideal treatment should not only utilise this capacity but also protect the kidneys.

This study had two major strengths. First, the follow-up duration was very long. This enabled examination of the incidence of ESRD that developed long after onset of diabetes. Second, all the variables were measured by paediatricians or internal medicine physicians specialising in diabetes. These measurements were conducted using the network of diabetes specialists in Hokkaido, enabling face-to-face communication. This study also had a few limitations. First, because of the lack of technology and practice for measurement of pancreatic autoantibodies at baseline, we could not diagnose the slowly progressive subtype using the current criteria. Second, because fulminant type 1 diabetes was first reported in the year 2000 and glycated haemoglobin was not routinely measured at baseline from 1959 to 1996, we were unable to distinguish fulminant type 1 diabetes from acute-onset type 1 diabetes in this cohort. Third, because the patient data were gathered from a single prefecture, the results may not represent those of all Japanese patients. Finally, the response rate of 75 % may be insufficient. The non-responders may have biased the results.

5. Conclusions

In this study, the incidence of ESRD was higher in patients with the slowly progressive than acute-onset subtype of type 1 diabetes. The comparisons of combinations of characteristics revealed that male sex and the slowly progressive subtype were associated with the highest incidence of ESRD. We were unable to clearly define the attributes that affect life expectancy after development of ESRD. We believe that the treatment strategy should be considered with attention to the risk of renal failure in patients with the slowly progressive subtype. Now that the definition of the slowly progressive subtype has been established, it is expected that more studies on the prognosis of this subtype will be performed.

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CRedit authorship contribution statement

Hiroshi Yokomichi: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Mie Mochizuki:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Shigeru Suzuki:** Writing – review & editing, Writing – original draft, Data curation. **Yoshiya Ito:** Writing – review & editing, Writing – original draft, Data curation. **Tomoyuki Hotsubo:** Writing – review & editing, Writing – original draft, Data curation. **Nobuo Matsuura:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization.

Ethics approval

The study protocol was reviewed and approved by the ethics committee of Hokkaido University Hospital (approval number: 019–0256). Attending physicians in the hospital or clinic explained the study to their patients and obtained verbal informed consent from the parent(s) or legal guardian(s) of each child and/or assent by the child (when applicable) before initiating the medical interview and record review.²¹

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Declaration of competing interest

The authors declare that they have no conflicts of interest regarding the present work.

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