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ORIGINAL ARTICLE

High risk of renal dysfunction in patients with fulminant type 1 diabetes

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Keywords
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ABSTRACT

Aims/Introduction: To compare the incidence rate of renal dysfunction between patients with fulminant type 1 diabetes and those with acute-onset type 1 diabetes.

Materials and Methods: The present retrospective cohort study included patients with fulminant type 1 diabetes and acute-onset type 1 diabetes diagnosed during April 1993 to March 2016 at a national center in Japan. Glycated hemoglobin levels, incidence rates of renal dysfunction defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 and microalbuminuria were examined.

Results: In total, 115 patients with type 1 diabetes (10 with fulminant type 1 diabetes and 105 with acute-onset type 1 diabetes) were included. The median glycated hemoglobin levels were significantly lower in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes 0, 3, 6 and 9 years after diabetes onset (6.5 vs 12.7%, 6.5 vs 7.9%, 6.7 vs 8.2%, 7.5 vs 8.5%, respectively). Kaplan–Meier analysis showed a significantly higher incidence rate of renal dysfunction in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes (hazard ratio 1.72, 95% confidence interval 1.01–2.97, $P = 0.037$). The incidence rate of microalbuminuria did not significantly differ between the groups (hazard ratio 0.97, 95% confidence interval 0.34–2.77, $P = 0.95$). Sensitivity analysis using age- and sex-matched patients with fulminant type 1 diabetes and acute-onset type 1 diabetes yielded similar results.

Conclusions: The risk of developing renal dysfunction is higher in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes, despite better glycemic control.

INTRODUCTION

Type 1 diabetes mellitus is characterized by insulin deficiency caused by pancreatic beta cell destruction[1]. Recently, a novel subtype of type 1 diabetes, known as 'fulminant type 1 diabetes,' and responsible for approximately 20% of all ketosis-onset type 1 diabetes cases in the Japanese population, was reported[2,3]. The clinical characteristics of fulminant type 1 diabetes are as follows: remarkably abrupt disease onset; very short duration (usually <1 week) of hyperglycemic symptoms, such as polyuria and thirst at the time of diagnosis; negative findings of islet-related autoantibodies, such as islet-cell antibodies, glutamic acid decarboxylase antibodies, insulin antibodies, anti-insulinoma-associated antigen 2 antibodies and zinc transporter 8 antibodies; virtually no C-peptide secretion; elevated serum pancreatic enzyme levels; frequent flu-like symptoms around the time of disease onset; association with pregnancy; and strong association with the human leukocyte antigen-DR4-DQ4 haplotype[2–5].

A previous study reported that patients with fulminant type 1 diabetes were at a higher risk of developing microalbuminuria than those with acute-onset type 1 diabetes[6], whereas another report showed that this risk did not differ between patients with fulminant type 1 diabetes and those with acute-onset type 1 diabetes[7]. However, currently, there are no studies that compare the risk of developing renal dysfunction in these patients. Therefore, the present study aimed to compare the incidence of renal dysfunction, defined as declining estimated glomerular

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filtration rate (GFR), between patients with fulminant type 1 diabetes and those with acute-onset type 1 diabetes over a prolonged period.

METHODS

Study design and patients

The present retrospective cohort study was carried out at the National Center for Global Health and Medicine in Tokyo, Japan. All patients diagnosed with fulminant type 1 diabetes or acute-onset type 1 diabetes at our hospital between 1 April 1993 and 31 March 2016 were included, and information was collected from their medical records. Patients with slowly progressive insulin-dependent diabetes mellitus or latent autoimmune diabetes were excluded from this study. A diagnosis of fulminant type 1 diabetes was made based on the following criteria[2]: ketosis or ketoacidosis for approximately 1 week after diabetes onset, blood glucose levels >288 mg/dL, glycated hemoglobin (HbA_{1c}) levels <8.5% at the initial visit, urine C-peptide <10 μg/day at the time of onset and fasting serum C-peptide <0.3 ng/mL or serum C-peptide <0.5 ng/mL after glucagon loading (or 2 h after a meal). Acute-onset type 1 diabetes was defined as follows[6]: the presence of ketoacidosis or ketosis at diabetes onset, hyperglycemic symptoms within the 3 months preceding initiation of insulin therapy, requiring insulin therapy after diabetes onset and the presence of at least one islet-related autoantibody (e.g., glutamic acid decarboxylase antibodies, insulin antibodies, anti-insulinoma-associated antigen 2 antibodies, zinc transporter 8 antibodies). Patients with estimated GFR <60 mL/min/1.73 m^2 at the time of diabetes onset were excluded. All eligible patients in the present study were followed until they left our hospital or died. The maximum follow-up period was 10 years after diagnosis of diabetes. This study was approved by the institutional review board of the National Center for Global Health and Medicine.

Measurements

The measured variables included age, sex, body mass index (calculated weight in kilograms divided by height in meters squared), systolic and diastolic blood pressure, antihypertensive medication use, dyslipidemia, plasma glucose, HbA_{1c}, serum C-peptide, serum creatinine levels, urinary albumin excretion and total daily insulin dose at the time of diabetes onset. Systolic and diastolic blood pressure, and antihypertensive medication use at the end of follow up were also assessed. The primary outcome of the present study was the incidence of renal dysfunction, defined as the first time when estimated GFR levels were <60 mL/min/1.73 m^2[8]. The secondary outcome was the incidence of microalbuminuria, defined as the first time when urinary albumin excretion was ≥30 mg/g creatinine in the absence of urinary tract infection and/or hematuria[6]. Dyslipidemia was defined as follows: triglycerides ≥150 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, low-density lipoprotein cholesterol ≥140 mg/dL (calculated using the Friedewald formula[9]), previous diagnosis of dyslipidemia or currently undergoing treatment with antidyslipidemic medications. Estimated GFR was calculated using the following formula[10]: estimated GFR (mL/min/1.73 m^2) = $194 \times (\text{serum creatinine level, } mg/dL)^{-1.094} \times (\text{age, years})^{-0.287}$ (×0.739 if the patient was a woman). A severe hypoglycemic episode was defined as the presence of any hypoglycemic symptoms that could not be resolved by the patients outside a hospital setting, and that required medical assistance after visiting the emergency room by ambulance[11]. Cardiovascular disease included angina, myocardial infarction, stroke and transient ischemic attack. Cancer was defined as any past history of malignant lesions.

Statistical analysis

The Mann–Whitney *U*-test was used to examine continuous variables, and the Fisher's exact test was used for categorical variables. Kaplan–Meier analysis with the log–rank test was used to compare the incidence rates of renal dysfunction and microalbuminuria between patients with fulminant type 1 diabetes and acute-onset type 1 diabetes. We also carried out a sensitivity analysis in age- and sex-matched patients with fulminant type 1 diabetes and acute-onset type 1 diabetes. We matched a patient with fulminant type 1 diabetes to five patients with acute-onset type 1 diabetes, resulting in a final sample of 60 patients (10 patients with fulminant type 1 diabetes and 50 with acute-onset type 1 diabetes). A P-value <0.05 was considered as statistically significant. All analyses were carried out using STATA software, version 11.1 (StataCorp, College Station, Texas, USA).

RESULTS

A total of 120 patients (12 patients with fulminant type 1 diabetes and 108 with acute-onset type 1 diabetes) met the inclusion criteria for the present study. Two patients with fulminant type 1 diabetes and three with acute-onset type 1 diabetes were excluded because their estimated GFR at diabetes onset were <60 mL/min/1.73 m^2, resulting in a final sample of 10 patients with fulminant type 1 diabetes and 105 with acute-onset type 1 diabetes. The median follow-up periods (interquartile range) were 4.87 years (3.62–9.41 years) in patients with fulminant type 1 diabetes, and 6.11 years (2.31–9.90 years) in those with acute-onset type 1 diabetes. The shortest follow-up periods were 0.13 and 0.15 years in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes, respectively. Table 1 shows the characteristics of patients with fulminant type 1 diabetes and acute-onset type 1 diabetes at diabetes onset. The female-to-male ratio was relatively lower in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes (20.0 vs 51.4%, $P = 0.06$). Some variables that reflect the pathophysiological status, such as serum C-peptide (0.10 ng/mL vs 0.69 ng/mL, $P < 0.001$) and HbA_{1c} levels (6.5 vs 12.7%, $P < 0.0001$) were significantly lower in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes. Age, body mass index, systolic and diastolic blood pressure, antihypertensive medication use, prevalence of dyslipidemia,

Table 1 | Baseline characteristics of fulminant type 1 diabetes and acute-onset type 1 diabetes at diabetes onset

	FT1D (n = 10)	AT1D (n = 105)	P
Age (years)	43 (31–56)	37 (16–52)	0.24
Female	2 (20.0%)	54 (51.4%)	0.06
BMI (kg/m^2)	20.5 (19.0–21.7)	19.1 (17.1–21.0)	0.18
Systolic BP (mmHg)	103.0 (100.0–110.0)	113.5 (104.0–123.0)	0.12
Diastolic BP (mmHg)	62.0 (54.0–66.0)	70.0 (60.0–76.0)	0.43
Antihypertensive medications			
ARB or ACE inhibitor	1 (10%)	6 (5.7%)	0.34
Calcium channel blocker	1 (10%)	7 (6.6%)	0.38
Beta-blocker	0 (0%)	1 (0.9%)	0.94
Alpha-blocker	0 (0%)	0 (0%)	–
Thiazide	0 (0%)	1 (0.9%)	0.94
Dyslipidemia	5 (50.0%)	24 (22.9%)	0.26
Plasma glucose (mg/dL)	711 (491–867)	425 (297–632)	0.06
HbA_{1c} (%)	6.5 (6.0–7.4)	12.7 (11.3–14.4)	<0.0001
Serum C-peptide (ng/mL)	0.10 (0.10–0.14)	0.70 (0.40–1.12)	0.0009
Estimated GFR (mL/min/1.73 m^2)	111.1 (83.3–124.1)	98.6 (80.5–115.4)	0.53
UAE (mg/g/Cre)	6.75 (4.18–7.00)	8.42 (4.76–17.53)	0.27
Total daily insulin dose (units/day)	33 (24–45)	27 (15–34)	0.10
Total daily insulin dose (units/kg/day)	0.53 (0.40–0.84)	0.51 (0.26–0.72)	0.41
CVD events	0 (0%)	0 (0%)	–
Cancer	0 (0%)	0 (0%)	–

Data are presented as n, n (%) or median (interquartile range). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Estimated glomerular filtration rate (GFR) was calculated using the following formula[10]: estimated GFR (mL/min/1.73 m^2) = 194 × (serum creatinine level, mg/dL)$^{-1.094}$ × (age, years)$^{-0.287}$ (×0.739 if the patient was a woman). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AT1D, acute-onset type 1 diabetes; BP, blood pressure; Cre, urinary creatinine level; CVD, cardiovascular disease; FT1D, fulminant type 1 diabetes; HbA_{1c}, glycated hemoglobin; UAE, urinary albumin excretion.

estimated GFR, urinary albumin excretion, total daily insulin dose, cardiovascular disease events, and cancer did not significantly differ between the groups.

The trends of HbA_{1c} levels in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes are shown in Figure 1. Median HbA_{1c} levels were significantly lower in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes 0, 3, 6, and 9 years after diabetes onset (6.5 vs 12.7%, 6.5 vs 7.9%, 6.7 vs 8.2%, 7.5 vs 8.5%, respectively). The number of patients who had experienced one or more severe hypoglycemic episodes was zero out of 10 (0%) in patients with fulminant type 1 diabetes and eight out of 105 (7.6%) in those with acute-onset type 1 diabetes. Systolic and diastolic blood pressure at the end of follow up was not significantly different between patients with fulminant type 1 diabetes and acute-onset type 1 diabetes (122 [104–142] mmHg vs 114 [102–126] mmHg, P = 0.34 and 70 [67–74] mmHg vs 67 [60–78] mmHg, P = 0.57, respectively). The rate of patients who achieved the blood pressure targets (systolic pressure <130 mmHg and diastolic pressure <70 mmHg[12]) at the end of the follow-up period was not significantly different between the two groups (7/10 [70.0%] vs 73/105 [69.5%] in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes, respectively; P = 0.59). Antihypertensive medication use at the end of follow up was not significantly different between the two groups (angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor: 1 [10.0%] vs 10 [9.5%], P = 0.47; calcium channel blocker: 0 [0%] vs 9 [8.5%], P = 0.44; beta-blocker: 0 [0%] vs 1 [1.0%], P = 0.81; alpha-blocker: 0 [0%] vs

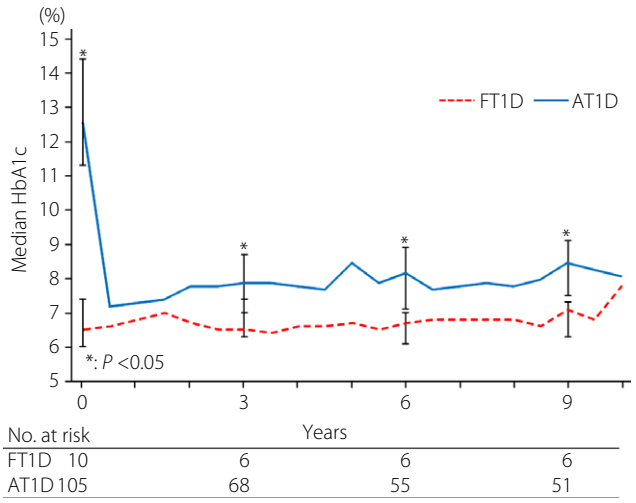

Figure 1 | Trends of glycated hemoglobin (HbA_{1c}) levels in fulminant type 1 diabetes (FT1D) and acute-onset type 1 (AT1D) diabetes for 10 years after diabetes onset.

0 [0%]; thiazide: 0 [0%] vs 0 [0%] in patients with fulminant type 1 diabetes or acute-onset type 1 diabetes, respectively). Furthermore, the use of antihypertensive medications did not significantly differ in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes (1/10 [10.0%] vs 9/105 [9.5%], respectively, $P = 0.61$).

Kaplan–Meier curves for the incidence rate of renal dysfunction in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes are shown in Figure 2. The incidence rate of renal dysfunction was significantly higher in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes (hazard ratio [HR] 1.72, 95% confidence interval [CI] 1.01–2.97, $P = 0.037$). The Kaplan–Meier curves in Figure 3 show the incidence rate of microalbuminuria in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes. No significant differences were observed between the two groups (HR 0.97, 95% CI: 0.34–2.77, $P = 0.95$). As a sensitivity analysis, we compared the incidence rate of renal dysfunction and microalbuminuria only in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes who were followed up for >1 year. This analysis did not change the overall results (the incidence rate of renal dysfunction was significantly higher in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes [HR 1.96, 95% CI: 1.12–3.43, $P = 0.015$], and the incidence rate of microalbuminuria was not significantly different between the two groups [HR 1.03, 95% CI: 0.35–2.97, $P = 0.96$]). We also compared the incidence rate of hematuria, defined as a positive dipstick result in two consecutive urine samples[13], in patients with estimated GFR levels of <60 mL/min/1.73 m^2. The incidence rate of hematuria in these patients was five out of 17 (29.4%). We also compared the incidence rate of hematuria between patients with fulminant type 1 diabetes and those with acute-onset type 1 diabetes, and

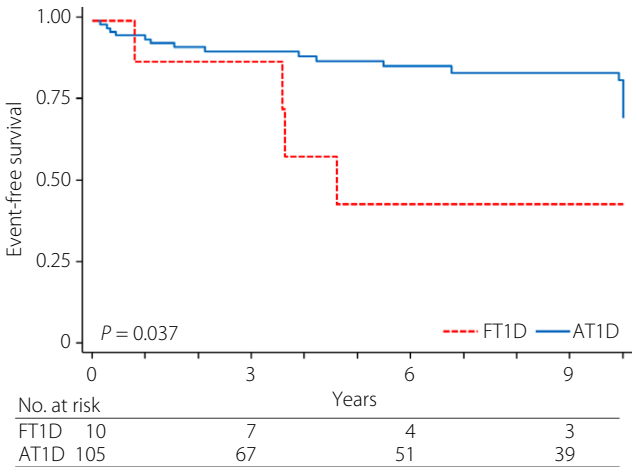

Figure 2 | Kaplan–Meier curves of the incidence rate of renal dysfunction in fulminant type 1 diabetes (FT1D) and acute-onset type 1 diabetes (AT1D).

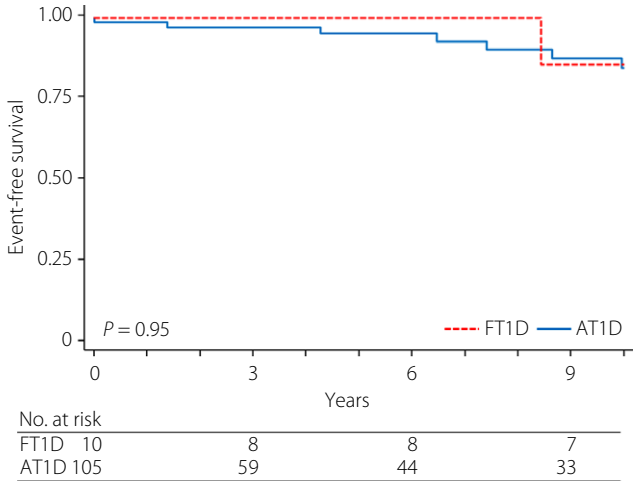

Figure 3 | Kaplan–Meier curves of the incidence rate of microalbuminuria in fulminant type 1 diabetes (FT1D) and acute-onset type 1 diabetes (AT1D).

the results of the Kaplan–Meier analysis showed no significant difference (HR 1.36, 95% CI: 0.79–2.35, $P = 0.24$).

Table S1 shows the baseline characteristics in the age- and sex-matched patients with fulminant type 1 diabetes and acute-onset type 1 diabetes. Variables except for plasma glucose, HbA_{1c}, and serum C-peptide levels did not significantly differ between age- and sex-matched patients with fulminant type 1 diabetes and acute-onset type 1 diabetes. Systolic and diastolic blood pressure at the end of follow up were not significantly different between patients with age- and sex-matched fulminant type 1 diabetes and acute-onset type 1 diabetes (122 [104–142] mmHg vs 110 [102–122] mmHg, $P = 0.31$ and 70 [67–74] mmHg vs 70 [60–78] mmHg, $P = 0.96$, respectively). Antihypertensive medication use at the end of follow up was not significantly different between the two groups (angiotensin II receptor blocker or angiotensin-converting enzyme inhibitor: 1 [10.0%] vs 6 [12.0%], $P = 0.59$; calcium channel blocker: 0 [0%] vs 2 [4.0%], $P = 0.78$; beta-blocker: 0 [0%] vs 0 [0%]; alpha-blocker: 0 [0%] vs 0 [0%]; thiazide: 0 [0%] vs 0 [0%] in patients with age- and sex-matched fulminant type 1 diabetes or acute-onset type 1 diabetes, respectively). The trends of HbA_{1c} levels were significantly lower in age- and sex-matched patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes (6.5 vs 12.7%, 6.3 vs 7.7%, 6.7 vs 7.7%, 7.1 vs 8.2% in 0, 3, 6, 9 years after diabetes onset, respectively), whereas the incidence rate of renal dysfunction was significantly higher in age- and sex-matched patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes (HR 2.94, 95% CI: 1.39–6.21, $P = 0.002$; Figure S1). The incidence rate of microalbuminuria did not differ significantly between the age- and sex-matched patients with fulminant type 1 diabetes and acute-onset type 1 diabetes (HR 0.76, 95% CI 0.26–2.20, $P = 0.60$; Figure S2).

DISCUSSION

To the best of our knowledge, this is the first study to report a higher risk of developing renal dysfunction in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes. The risk of microalbuminuria was not significantly different between the two groups.

The Diabetes Control and Complications Trial Research Group reported that intensive blood glucose control can prevent the development of microvascular complications in patients with type 1 diabetes[14]. Diabetic nephropathy usually starts with microalbuminuria[15]. There are two studies that compared the development of microvascular complications in patients with fulminant type 1 diabetes to those with acute-onset type 1 diabetes. Murase *et al.*[6] reported that the incidence rate of microalbuminuria was higher in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes because of unstable glycemic control caused by depleted and irreversible loss of insulin production, and frequent severe hypoglycemic episodes. Conversely, Takaike *et al.*[7] reported that no significant differences in the development of microalbuminuria were observed between patients with fulminant type 1 diabetes and those with acute-onset type 1 diabetes. Furthermore, they reported that the mean HbA_{1c} levels were significantly lower in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes, and the frequency of severe hypoglycemic episodes did not significantly differ between the two groups. They speculated that microvascular complications were prevented as a result of good glycemic control in patients with fulminant type 1 diabetes. In the present study, HbA_{1c} levels were significantly lower and the frequency of hypoglycemic episodes were less in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes, and the incidence rate of microalbuminuria did not significantly differ between the two groups. However, the incidence rate of renal dysfunction was significantly higher in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes, and the same results were observed even after matching the two groups by age and sex. Considering the significantly better glycemic control in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes, a possible explanation for this could be the differences in the pathophysiological mechanism at diabetes onset between fulminant type 1 diabetes and acute-onset type 1 diabetes. In a previous report, immunoglobulin A antibody titers to enteroviruses, such as coxsackie A, coxsackie B, polioviruses and echoviruses, were significantly higher in patients with recent-onset fulminant type 1 diabetes than in those with acute-onset type 1 diabetes, and these viruses are thought to be one of the causes of fulminant type 1 diabetes[16]. Several studies have focused on the relationship between viral infection and renal injury[17–20], and enteroviruses were recently established as causative agents in glomerulonephritis[21]. The infection by enteroviruses at diabetes onset might be associated with the risk of renal dysfunction in fulminant type 1 diabetes.

The present study results showed that the incidence rate of renal dysfunction was significantly higher in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes, and we found no significant differences in the incidence rates of microalbuminuria and hematuria in patients with fulminant type 1 diabetes and acute-onset type 1 diabetes. A previous fundamental study in macaques with group B coxsackievirus infection reported that hematuria, albuminuria and histopathological changes in the kidneys suggested that glomerulonephritis developed nearly simultaneously after viral infection[22]. However, the association among the development of renal dysfunction, microalbuminuria and hematuria remains unknown in patients with glomerulonephritis caused by viruses.

The present study had several limitations. First, this retrospective study was carried out at a single national center, and the small sample size and some missing data might have influenced the results. In addition, just a few participants underwent evaluations for viral antibodies, urinary casts, renal interstitial markers and nephrosclerosis assessed by imaging procedures. Therefore, it could be speculated that patients with fulminant type 1 diabetes developed renal dysfunction because of viral involvement. Second, although we do not know why patients with fulminant type 1 diabetes achieved good glycemic control without severe hypoglycemia, a possible explanation is that the severe hypoglycemic episodes were retrospectively confirmed using questionnaires, and several episodes were missed. Therefore, a large-scale, multicenter, prospective study without missing data is required to confirm the results.

We report that the incidence rate of renal dysfunction was significantly higher in patients with fulminant type 1 diabetes than those with acute-onset type 1 diabetes, even if blood glucose control was significantly better in patients with fulminant type 1 diabetes. Further studies are required to reveal the pathophysiological factors responsible for the higher risk of developing renal dysfunction in patients with fulminant type 1 diabetes than in those with acute-onset type 1 diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

Figure S1 | Kaplan–Meier curves of the incidence of renal dysfunction in age- and sex-matched patients with fulminant type 1 diabetes (FT1D) and acute-onset type 1 diabetes (AT1D).

Figure S2 | Kaplan–Meier curves of the incidence rate of microalbuminuria in age- and sex-matched patients with fulminant type 1 diabetes (FT1D) and acute-onset type 1 diabetes (AT1D).

Table S1 | Baseline characteristics in age- and sex-matched patients with FT1D and AT1D at diabetes onset.