Original Article

Rapid increase in the incidence of end-stage renal disease in patients with type 1 diabetes having HbA1c 10% or higher for 15 years

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Abstract. The incidence of end-stage renal disease (ESRD) in Japanese patients with type 1 diabetes mellitus (T1DM) was investigated regarding the association between mean HbA1c values during follow-up and the duration of follow-up/illness. The study includes 988 patients diagnosed at ages younger than 30 yr. These patients were initially examined between 1962 and 1999, and HbA1 and/or HbA1c measurements were taken for at least 3 yr after 1980. The follow-up period was from the date of the first HbA1 or HbA1c measurement to the final measurement day, or HbA1c measurement day immediately before the development of ESRD. The condition progressed to ESRD in 63 patients (mean duration of illness: 23.6 yr). Cox regression analysis revealed that patients with HbA1c of ≥ 10% had a significantly increased higher risk than those with HbA1c under 8% (P < 0.0001). The HbA1c cut-off point was 10.0%. The HbA1c value was ≥ 10% at baseline and during follow-up in 128 patients. Assuming that HbA1c of ≥ 10% persisted since the time of diagnosis in these patients, the cumulative incidence of ESRD abruptly increased after 15 yr of illness. Thus, the incidence of ESRD increased after the persistence of HbA1c of ≥ 10% for 15 yr.

Key words: type 1 diabetes mellitus (T1DM), end-stage renal disease (ESRD), HbA1c, follow-up period, duration of diabetes

Introduction

Diabetic kidney disease (DKD) is the main etiological factor for end-stage renal disease (ESRD). In Europe, the United States, and Japan, it accounts for at least 40% of cases of new-onset ESRD. Further, the risk of ESRD is high in patients with type 1 diabetes mellitus (T1DM) (1, 2).

However, the cumulative risk of ESRD in patients with T1DM has decreased markedly

over time. In Finland, the relative risk of ESRD was 0.13 (95% confidence interval [CI] 0.08–0.22) in patients diagnosed in 1995–2011 compared with those diagnosed in 1965–1979, and the incidence rate of ESRD started to rise 15 yr after they were diagnosed with diabetes (3). We have previously investigated whether the incidence of ESRD in patients with T1DM depends on the year of T1DM diagnosis and found that its incidence in more recently diagnosed T1DM patients (1985–1999 diagnosis group) was markedly lower than that in patients diagnosed in 1961–1984 (4). In the former group of patients, the systolic blood pressures at the time of registration and during the follow-up period, as well as the hemoglobin A1c (HbA1c) values during the follow-up period, were significantly lower, suggesting that these factors are associated with a lower incidence of ESRD.

In the current study, we examined the association between the incidence of ESRD and the mean HbA1c values during follow-up in patients with T1DM. In addition, the HbA1c cut-off point indicating the risk of ESRD was determined by employing the Contal and O'Quigley method (5). Furthermore, the incidence of ESRD in patients with T1DM was investigated with regard to the association between the mean HbA1c values during follow-up and the duration of follow-up/illness.

Subjects and Methods

Patient recruitment

The study recruited 988 patients (358 males and 630 females) diagnosed with T1DM at <3 0 yr of age between 1961 and 1999. These patients visited the Tokyo Women's Medical University Hospital for their initial consultation between 1962 and 1999, and they had HbA1 or HbA1c measurements for at least 3 yr after 1980. To investigate the association between the cumulative incidence of ESRD and HbA1c, they were separated into five groups based on their mean HbA1c values during follow-up (Group A:

< 8%, Group B: 8.0–8.9%, Group C: 9.0–9.9%, Group D: 10.0–10.9%, and Group E: ≥ 11.0%). We excluded patients who were diagnosed with ESRD at the time of registration or within 1 yr after registration (n = 18) and those with ESRD related to kidney disease other than DKD (n = 3).

A diagnosis of T1DM was made according to the classification and diagnostic criteria of diabetes mellitus proposed by the Japan Diabetes Society (JDS) (6, 7). After serum C-peptide and anti-glutamic acid decarboxylase (GAD) antibody tests became available, the disease type was classified based on these test results. However, we excluded anti-GAD-antibody-positive patients who had not required insulin therapy for a few years.

Measurement

The levels of glycated hemoglobin were measured using the mini-column method (Isolab [Quik-Sep], Akron, OH, USA) from 1980 to 1981, the glycospec method (Abbott [ABA-200], North Chicago, IL, USA) from 1982 to March, 1983, and high-performance liquid chromatography (HPLC; A8120, HA8121, HA8131, HA8150, HA8160, HA8180: ARKRAY, Kyoto, Japan) from April, 1983 to the present. The values by the mini-column method $[x1]$ and the glycospec method $[x2]$ were converted to HPLC $[y]$ values using the following formulae: $[y] = ([x1] + 0.302)/1.179$ $[r = 0.990]$ and $[y] = ([x2] + 2.151)/1.332$ $[r = 0.855]$. Finally, all values were expressed as glycated hemoglobin A1c (HbA1c) values (%) as certified by the National Glycohemoglobin Standardization Program (NGSP) (8). Systolic blood pressure was measured after resting for five minutes or longer at the outpatient clinic during each visit since baseline.

The annual mean HbA1c values and systolic blood pressure were calculated, and in addition, the mean values during the follow-up period were calculated. The urinary protein levels were semi-quantified using Albustix (Miles-Sankyo, Tokyo, Japan). Patients with protein in their urine on three consecutive visits were regarded as having

proteinuria. Diabetic retinopathy was diagnosed by ophthalmologists through dilated pupils.

Follow-up

ESRD was defined as the initiation of any type of renal replacement therapy (hemodialysis, peritoneal dialysis, and kidney transplantation) or rejection of these modalities. The diabetes follow-up period was calculated from the date of the first HbA1 or HbA1c measurement (baseline) to the final measurement day (December 31, 2010) or the measurement day immediately before developing ESRD. The endpoint was set as the development of ESRD.

Based on medical records, we investigated the presence of therapy using renin-angiotensin inhibitors or statins at baseline and during the follow-up period.

Statistical analysis

The data were expressed as the mean ± standard deviation (SD). For statistical analysis, the incidence was presented as the number of patients with disease onset per 1,000 person-years. One-way ANOVA and the Chi-squared test (or Jonckheere-Terpstra trend test and Cochran-Armitage trend test) were used to compare continuous and categorical data, respectively. In patients with events (ESRD or death), the follow-up period was regarded as the interval from registration until the date of occurrence of an event. In those without events, it was regarded as the interval from baseline until completion of the follow-up survey (December 31, 2010). For those who discontinued visiting the outpatient clinic in the absence of ESRD, the follow-up period was calculated as the interval from baseline until the final day of HbA1c measurement.

We compared the cumulative incidences of ESRD among the five groups, which were established based on the mean HbA1c values during the follow-up period, using the Kaplan-Meier method with the log-rank test. The diabetes follow-up period from baseline was used as the interval until event occurrence. In patients registered before 1979, as neither HbA1 nor HbA1c had been measured at that time, the HbA1c value (NGSP-converted value) converted from the initial HbA1 value in 1980 was adopted as the baseline value. In addition, for patients registered before 1979, the initial date of HbA1 or HbA1c measurement was used as the baseline. Furthermore, the cumulative incidence of ESRD was plotted using the Kaplan-Meier method with the log-rank test, according to the duration of follow-up/illness (pre-pubertal vs. post-pubertal onset of T1DM [from 11- and 9-yr-old in males and females, respectively]) (9).

We explored the hazard ratio of each risk factor by Cox regression analysis (risk factors: gender, age at diagnosis, calendar year of baseline [< 1990 vs. ≥ 1990]) (Health insurance coverage of self-monitored blood glucose and the use of human pharmaceutical insulin were enabled in 1986. Intensive insulin therapy was first performed in 1990), duration at baseline, proteinuria at baseline, retinopathy at baseline, mean values of systolic blood pressure during follow-up, mean values of HbA1c during follow-up, and groups according to mean values of HbA1c during follow-up). Univariate and multivariate Cox regression analyses were used to compute the hazard ratios and 95% CI to assess the effects of covariates on the onset of ESRD. The gender, age at diagnosis, calendar year of baseline, duration of T1DM at baseline, proteinuria at baseline, retinopathy at baseline in model A, mean systolic blood pressure, and HbA1c values during follow-up were added to model B1. Model B1 was modified to model B2 by replacing the mean values of HbA1c during follow-up with the categorical groups according to the mean values of HbA1c during follow-up.

Contal and O'Quigley analysis was conducted to investigate the association between ESRD and HbA1c, and a cut-off point for HbA1c was calculated.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute,

Inc., Cary, NC, USA).

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki 1964 and later versions. This study was approved by the Tokyo Women's Medical University School of Medicine Ethical Review Board (Approval day: Jan 16, 2017, No. 4,233).

Results

Baseline clinical characteristics of the subjects

The clinical characteristics of the 988 subjects are shown in Table 1. The numbers of patients in groups A, B, C, D, and E were 366, 290, 171, 96, and 65, respectively. There were no significant differences in gender, duration of disease, the prevalence of retinopathy, or systolic blood pressure among the five groups at baseline. Furthermore, no patient was taking renin-angiotensin system inhibitors (RASI) and/or statins at baseline.

Results of follow-up

The mean follow-up period was 17 yr, with a follow-up rate of 89% (Table 1). Among the 988 patients, the numbers for ESRD, death, ESRD and death, and loss of follow-up were 63 (6.4%; 20 males and 43 females), 61 (6.2%), 20 (2.0%), 107 (10.8%), respectively. The remaining 777 patients (78.6%) completed the follow-up. There was no significant difference in the status of confirmed ESRD and death, or in the mean systolic blood pressure during follow-up in the groups A, B, C, D, and E. The mean time from diagnosis of diabetes to ESRD was 23.6 yr (range 12.3–43.8). ESRD developed in only four (6.3%) of 63 ESRD patients in less than 15 yr since the diagnosis of diabetes. The overall incidence of ESRD (/1,000 person-years) (95% CI) was 3.9 (3.0–5.0) (Table 2). The overall incidences in groups A, B, C, D, and E were 1.3 (0.5–2.7),

1.8 (0.8–3.3), 3.4 (1.8–5.9), 10.2 (5.7–16.8), and 26.5 (16.3–40.7), respectively; the incidence of ESRD increased with an increase in the values of HbA1c.

The distribution of the cohort according to HbA1c at baseline and the mean HbA1c during the follow-up period in groups A to E are shown in Table 3A. The number of patients in whom HbA1c at baseline was greater than 10% was 504 (51.0%), but the number of patients with HbA1c values greater than the mean during the follow-up period decreased to 161 (16.3%). The mean number of measurements of HbA1c in the follow-up period was 115.3 ± 78.3.

Cumulative incidence of ESRD

The cumulative incidence of ESRD in the five groups significantly increased (P < 0.0001 [log-rank test], Fig. 1). In groups A, B, and C, the cumulative incidence of ESRD were nearly equal (1–5% at 15 yr of follow-up). The cumulative incidences of ESRD in groups D and E were higher than in groups A, B, and C (11% in group D and 31% in group E at 15 years of follow-up).

Cox regression analyses of variables associated with ESRD incidence

Univariate and multivariate Cox regression analyses exploring the effects of variables on the onset of ESRD are shown in Table 4. The mean values of HbA1c during follow-up and the groups according to the mean HbA1c values during follow-up had a significant association with the onset of ESRD, and this association was independent of gender, age, calendar year, duration, proteinuria at baseline, retinopathy at baseline, RASI use, and mean systolic blood pressure during follow-up (model B1 and B2). The mean HbA1c values during follow-up in groups C, D, and E were significantly associated with the onset of ESRD, as compared with group A (model B2). Groups D and E had especially high risks of ESRD.

Table 1. Baseline features and results of follow-up including, follow-up rate, data at follow-up, and number of type I diabetes mellitus (T1DM) patients with end-stage renal disease (ESRD) according to the mean values of glycated hemoglobin (HbAlc) during follow-up

| | Mean values of HbA1c during follow-up (%) | | | | | | P-value |
	Overall (N = 988)	A) < 8.0 (N = 366)	B) 8.0–8.9 (N = 290)	C) 9.0–9.9 (N = 171)	D) 10.0–10.9 (N = 96)	E) 11.0 ≤ (N = 65)	
Male (%)	358 (36.2%)	125 (34.2%)	111 (38.3%)	69 (40.4%)	32 (33.3%)	21 (32.3%)	NS
Age at diagnosis (yr)	14.6 ± 7.7	15.2 ± 7.7	15.0 ± 7.8	13.3 ± 7.8	13.8 ± 7.0	14.2 ± 7.3	< 0.05
Age at baseline (yr)	20.8 ± 8.1	21.6 ± 8.0	21.0 ± 8.0	19.4 ± 8.4	19.2 ± 7.9	21.6 ± 7.7	< 0.01
Calendar year of baseline							
1980–1989, N (%)	451 (45.6%)	101 (27.6%)	139 (47.9%)	122 (71.3%)	51 (53.1%)	38 (58.5%)	< 0.0001
1990–1999, N (%)	537 (54.4%)	265 (72.4%)	151 (52.1%)	49 (28.7%)	45 (46.9%)	27 (41.5%)	
Duration of diabetes at baseline (yr)	6.3 ± 6.4	6.4 ± 7.3	6.2 ± 6.0	6.1 ± 5.5	5.7 ± 5.2	7.4 ± 6.3	NS
Proteinuria at baseline, N (%)	52/962 (5.4%)	11/356 (3.1%)	15/282 (5.3%)	9/167 (5.4%)	6/94 (6.4%)	11/63 (17.5%)	< 0.01
Retinopathy at baseline, N (%)	235/947 (24.8%)	74/351 (21.1%)	68/279 (24.4%)	43/163 (26.4%)	28/93 (30.1%)	22/61 (36.1%)	NS
HbA1c at baseline (%)	10.4 ± 2.8	9.3 ± 2.6	10.2 ± 2.5	11.4 ± 2.5	11.8 ± 2.3	12.9 ± 2.8	< 0.0001
Systolic BP at baseline (mmHg)	113.0 ± 15.2	114.5 ± 15.2	112.4 ± 14.8	111.0 ± 15.9	111.3 ± 13.8	114.8 ± 15.5	NS
Status confirmed for ESRD and death (N, %)	881 (89.2%)	326 (89.1%)	261 (90.0%)	158 (92.4%)	83 (86.5%)	53 (81.5%)	NS
Year of follow-up (yr)	16.5 ± 8.4	14.7 ± 7.3	17.7 ± 8.9	20.6 ± 8.6	15.3 ± 7.8	11.6 ± 7.8	< 0.0001
Age at the end of follow-up (yr)	37.1 ± 9.9	36.2 ± 9.5	38.5 ± 10.4	39.7 ± 9.8	34.3 ± 8.5	32.9 ± 9.6	< 0.0001
Mean values of HbA1c during the follow-up (%)	8.6 ± 1.4	7.3 ± 0.5	8.4 ± 0.3	9.4 ± 0.3	10.4 ± 0.3	12.1 ± 1.1	< 0.0001
Mean values of systolic BP during the follow-up (mmHg)	121.6 ± 10.6	121.1 ± 10.1	122.5 ± 10.6	121.2 ± 10.3	122.1 ± 11.7	120.5 ± 12.2	NS
RASI use at follow-up, N (%)	186/978 (19.0%)	39/364 (10.7%)	57/288 (19.8%)	48/169 (28.4%)	24/94 (25.5%)	18/63 (28.6%)	< 0.0001
Statin use at follow-up, N (%)	108/977 (11.1%)	22/364 (6.0%)	29/288 (10.1%)	30/169 (17.8%)	10/94 (10.6%)	17/62 (27.4%)	< 0.0001
Current smoker at follow-up, N (%)	187/799 (23.4%)	41/270 (15.2%)	57/234 (24.4%)	50/158 (31.6%)	28/81 (34.6%)	11/56 (19.6%)	< 0.01
ESRD (N, %)	63 (6.4%)	7 (1.9%)	9 (3.1%)	12 (7.0%)	15 (15.6%)	20 (30.8%)	< 0.0001
Mean time from diagnosis of diabetes to ESRD (yr)	23.6 ± 7.4	27.7 ± 10.2	22.5 ± 4.7	27.6 ± 8.1	23.4 ± 6.5	20.4 ± 6.2	< 0.05
[Range (yr)]	[12.3–43.8]	[14.6–43.8]	[18.4–32.1]	[12.3–38.3]	[15.3–35.7]	[13.6–37.9]	

BP, blood pressure; RASI, renin-angiotensin inhibitors. The baseline used was the day of initial HbA1 or HbAlc measurement. The endpoint used was the day of ESRD onset. P-value: One-way ANOVA and the Chi-squared test (or Jonckheere-Terpstra trend test and Cochran-Armitage trend test) were used to compare continuous and categorical data, respectively.

Table 2. Incidence of end-stage renal disease (ESRD) according to mean glycated hemoglobin (HbAlc) in follow-up

	Mean values of HbA1c during follow-up (%)				
	A) < 8.0	B) 8.0–8.9	C) 9.0–9.9	D) 10.0–10.9	E) 11.0 ≤
N	366	290	171	96	65
Year of follow-up (yr)	14.7 ± 7.3	17.7 ± 8.9	20.6 ± 8.6	15.3 ± 7.8	11.6 ± 7.8
Onset of ESRD (N, %)	7 (1.9%)	9 (3.1%)	12 (7.0%)	15 (15.6%)	20 (30.8%)
Person-years of follow-up for ESRD	5,389	5,136	3,526	1,469	754
Incidence of ESRD (95%CI, /1,000 person-yr)	1.3 (0.5–2.7)	1.8 (0.8–3.3)	3.4 (1.8–5.9)	10.2 (5.7–16.8)	26.5 (16.3–40.7)
P-value		0.65	0.07	< 0.0001	< 0.0001
RR* (95%CI)	1	1.3 (0.5–3.6)	2.6 (1.0–6.6)	7.9 (3.2–19.2)	20.4 (8.7–48.1)

RR, relative risk; CI, confidence interval. P-value: Cox regression analysis using univariate analysis. * Relative risk of incidence of ESRD in each group when we measured A group reference = 1.

Table 3. Distribution of cohort according to glycated hemoglobin (HbAlc) at baseline and the mean values of HbAlc during follow-up

A

HbA1c (%)	Baseline (%)		Mean values of HbA1c during follow-up									
			Group A (< 8.0)		Group B (8.0–8.9)		Group C (9.0–9.9)		Group D (10.0–10.9)		Group E (11.0 ≤)	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
< 8.0	201	20.3	134	66.7	50	24.9	12	6.0	2	1.0	3	1.5
8.0–8.9	145	14.7	65	44.8	52	35.9	17	11.7	9	6.2	2	1.4
9.0–9.9	138	14.0	56	40.6	49	35.5	16	11.6	11	8.0	6	4.3
10.0–10.9	125	12.7	31	24.8	44	35.2	30	24.0	15	12.0	5	4.0
11.0–11.9	107	10.8	23	21.5	28	26.2	32	29.9	18	16.8	6	5.6
12.0–12.9	84	8.5	13	15.5	28	33.3	23	27.4	9	10.7	11	13.1
13.0–13.9	69	7.0	17	24.6	15	21.7	15	21.7	13	18.8	9	13.0
14.0 ≤	119	12.0	27	22.7	24	20.2	26	21.8	19	16.0	23	19.3
Total	988	100.0	366	37.0	290	29.4	171	17.3	96	9.7	65	6.6

B

HbA1c (%)	Baseline (%)		Mean values of HbA1c during follow-up (%)			
			–9.9		10.0–	
	No.	(%)	No.	(%)	No.	(%)
–9.9	484	49.0	451	45.6	33	3.3
10.0–	504	51.0	376	38.1	128	13.0
Total	988	100.0	827	83.7	161	16.3

A. Distribution of cohort according to HbAlc at baseline and the mean values of HbAlc during follow-up in groups A to E. P-value: Cochran-Armitage trend test in groups A to E. P < 0.0001.
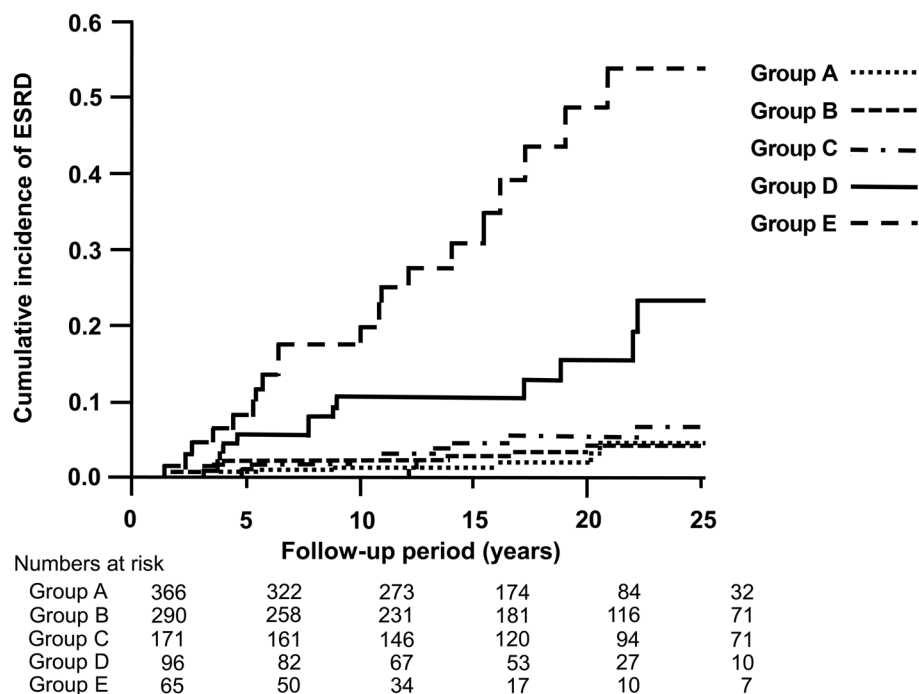B. Distribution of HbAlc at baseline and during follow-up divided at 10%.

Fig. 1. Cumulative incidence of end-stage renal disease (ESRD) according to the mean glycated hemoglobin (HbA1c) value during follow-up. Group A: < 8.0%, Group B: 8.0–8.9%, Group C: 9.0–9.9%, Group D: 10.0–10.9%, and Group E: ≥ 11.0%. Overall: P < 0.0001 (log-rank test).

Contal and O'Quigley analyses of the association between ESRD and HbA1c

The association between ESRD and HbA1c was examined by Contal and O'Quigley analysis. The cut-off point of HbA1c was 10.0%.

Cumulative incidence of ESRD assuming that HbA1c of 10% or higher persisted from the time of diagnosis in patients with HbA1c of 10% or higher at baseline and during follow-up

Of the 484 patients with HbA1c below 10% at baseline, there were only 33 with ≥ 10% HbA1c during follow-up (Table 3B). In contrast, the number of patients with ≥ 10% HbA1c during follow-up was 128 (H-HbA1c) among the 504 patients with ≥ 10% HbA1c at baseline. We considered these 128 patients to have had ≥ 10% HbA1c persistently since the time of diagnosis.

When we used the follow-up period as the x-axis, the cumulative incidence of ESRD in patients with H-HbA1c abruptly increased at three years of follow-up (Fig. 2A). The cumulative incidence of ESRD in patients with H-HbA1c was significantly higher than that in patients with HbA1c below 10% at baseline and during follow-up (L-HbA1c) (P<0.0001 by log-rank test). The cumulative incidence of ESRD in post-pubertal onset T1DM was significantly higher than that in pre-puberty onset T1DM (P = 0.0402 [log-rank test], Fig. 2B).

When we used the duration of illness as the x-axis, the cumulative incidence of ESRD in patients with H-HbA1c abruptly increased at 15 yr of illness using the Kaplan-Meier method (Fig. 2C). The cumulative incidence of ESRD in patients with H-HbA1c was significantly higher than that in patients with L-HbA1c (P < 0.0001 by log-rank test). The cumulative incidence of ESRD in post-pubertal onset T1DM was significantly higher than that in pre-puberty onset T1DM (P = 0.0160 [log-rank test], Fig. 2D).

Table 4. Cox regression analysis to explore the effect of gender, age at diagnosis (per yr), calendar yr of baseline (< 1990 vs. 1990 <), duration of type 1 diabetes mellitus (T1DM) at baseline (per yr), proteinuria at baseline, retinopathy at baseline, renin-angiotensin inhibitors (RASI) use at follow-up, mean values of systolic blood pressure (BP) during follow-up (per mmHg), mean values of glycated hemoglobin (HbAlc) during follow-up (%), and groups according to mean values of HbAlc during follow-up (per %)

| | Univariate analysis | | Multivariate analysis | | | | | |
| | | | Model A | | Model B1 | | Model B2 | |
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Male (vs. female)	0.77 (0.45–1.30)	0.34	0.69 (0.35–1.26)	0.24	0.79 (0.38–1.54)	0.50	0.69 (0.33–1.35)	0.29
Age at diagnosis	1.01 (0.98–1.05)	0.39	1.03 (0.99–1.07)	0.14	1.06 (1.01–1.10)	0.01	1.05 (1.01–1.10)	0.02
Calendar year of baseline < 1990 vs. 1990 ≤	0.99 (0.57–1.75)	0.97	1.26 (0.67–2.45)	0.48	0.80 (0.41–1.62)	0.53	0.74 (0.37–1.51)	0.40
Duration at baseline	1.14 (1.11–1.18)	< 0.0001	1.03 (0.97–1.09)	0.32	1.05 (0.98–1.12)	0.16	1.05 (0.98–1.13)	0.14
Proteinuria at baseline	19.65 (11.29–33.70)	< 0.0001	7.41 (3.85–14.39)	< 0.0001	5.83 (2.82–11.89)	< 0.0001	6.75 (3.13–14.56)	< 0.0001
Retinopathy at baseline	10.36 (5.59–20.59)	< 0.0001	4.02 (1.71–9.71)	0.0014	4.31 (1.70–11.39)	0.0021	4.92 (1.95–12.92)	0.0007
RASI use at follow-up	1.53 (0.87–2.59)	0.14			0.94 (0.48–1.77)	0.84	1.12 (0.57–2.15)	0.73
Mean values of systolic BP during follow-up	1.08 (1.05–1.10)	< 0.0001			1.03 (1.00–1.06)	0.03	1.01 (0.98–1.04)	0.52
Mean values of HbA1c during follow-up	1.89 (1.65–2.17)	< 0.0001			2.22 (1.85–2.68)	< 0.0001		
Groups according to mean values of HbA1c during follow-up		< 0.0001						< 0.0001
Group A	1						1	
Group B	1.26 (0.47–3.54)	0.65					1.44 (0.42–5.67)	0.57
Group C	2.37 (0.94–6.43)	0.07					3.85 (1.22–14.53)	0.02
Group D	7.73 (3.26–20.26)	< 0.0001					16.75 (5.45–63.19)	< 0.0001
Group E	20.69 (9.15–52.78)	< 0.0001					31.91 (10.89–117.19)	< 0.0001

ESRD, end-stage renal disease; HR, hazard ratio; CI, confidence interval. Values included in the multivariate analysis were as follows: Model A: gender, age at diagnosis (per yr), calendar yr of baseline (< 1990 vs. 1990 ≤), duration of T1DM at baseline (per yr), proteinuria at baseline, and retinopathy at baseline. Model B1: gender, age at diagnosis (per yr), calendar yr of baseline (< 1990 vs. 1990 ≤), duration of TIDM at baseline (per yr), proteinuria at baseline and retinopathy at baseline, RASI use at follow-up, mean values of systolic BP during follow-up (mmHg), and mean values of HbAlc during follow-up (%). Model B2: gender, age at diagnosis (per yr), calendar yr of baseline (< 1990 vs. 1990 ≤), duration of TIDM at baseline (per yr), proteinuria at baseline and retinopathy at baseline, RASI use at follow-up, mean values of systolic BP during follow-up (mmHg), and groups according to mean values of HbAlc during follow-up (%). P-value: Cox regression analysis.
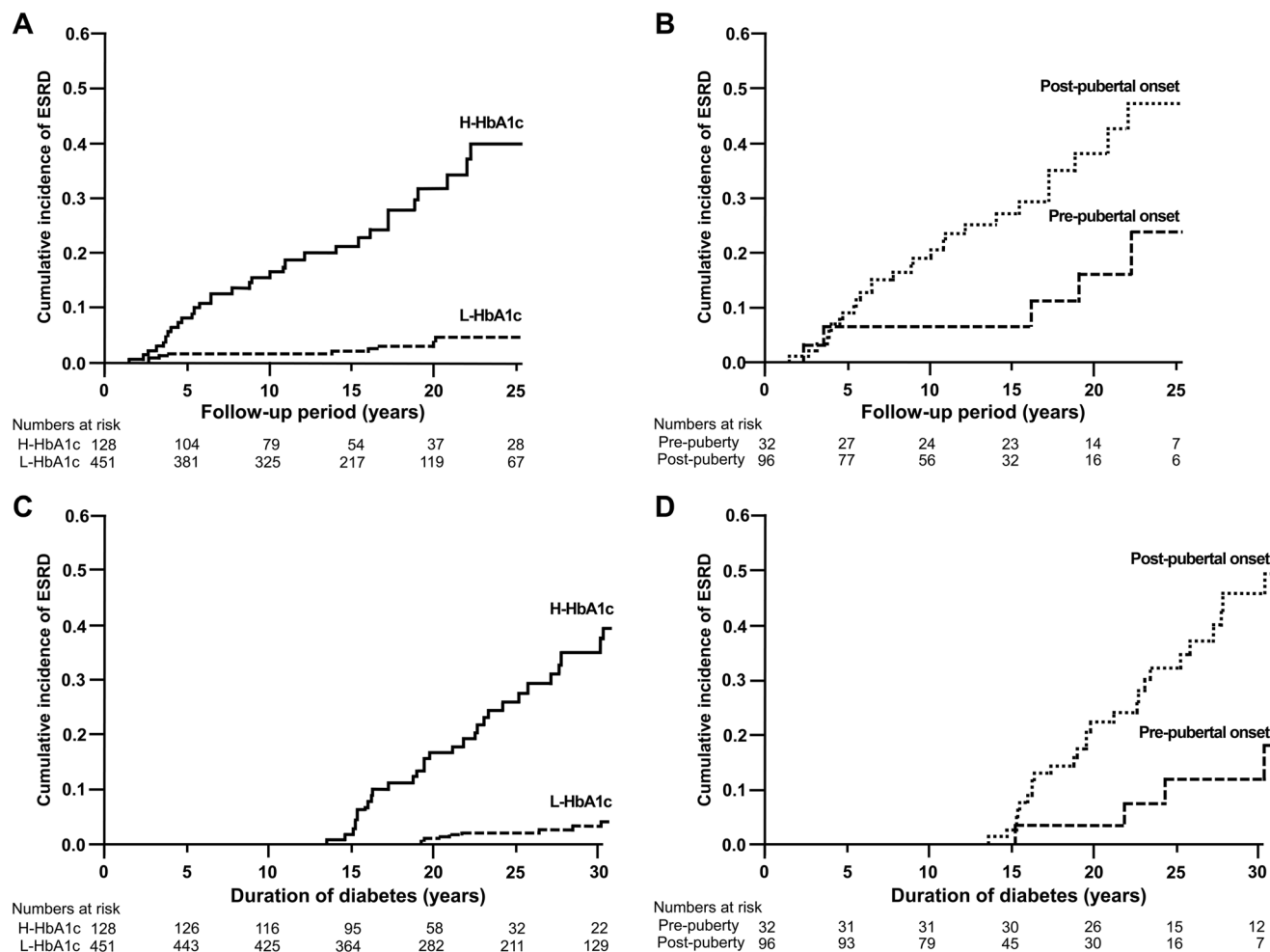
Fig. 2. Cumulative incidence of end-stage renal disease (ESRD) based on the assumption that glycated hemoglobin (HbA1c) of 10% or higher persisted since the time of diagnosis in patients with HbA1c of 10% or higher at initiation and during follow-up (H-HbA1c). X-axis = follow-up period (A and B), X-axis = duration of type 1 diabetes mellitus (T1DM) (C and D).

A: H-HbA1c (N = 128) and patients with HbA1c of 10% or lower at initiation and during follow-up (L-HbA1c, N = 451). The cumulative incidence of ESRD in patients with H-HbA1c abruptly increased after 3 yr of follow-up. The cumulative incidence of ESRD in patients with H-HbA1c was significantly higher than that in patients with L-HbA1c (P < 0.0001 by log-rank test).

B: Cumulative incidence of ESRD comparing pre-pubertal onset T1DM (N = 32) with post-pubertal onset (N = 96). The cumulative incidence of ESRD with the post-pubertal onset of T1DM was significantly higher than in those with the pre-pubertal onset (P = 0.0402 by log-rank test). X-axis = duration of T1DM (C and D).

C: H-HbA1c (N = 128) and L-HbA1c (N = 451). The cumulative incidence of ESRD in patients with H-HbA1c abruptly increased at 15 yr of illness. The cumulative incidence of ESRD in patients with H-HbA1c was significantly higher than that in patients with L-HbA1c (P < 0.0001 by log-rank test).

D: Cumulative incidence of ESRD comparing pre-pubertal onset T1DM (N = 32) with post-pubertal onset (N = 96). The cumulative incidence of ESRD in post-pubertal onset T1DM was significantly higher than that in pre-pubertal onset (P = 0.0160 by log-rank test).

Discussion

We investigated the target value for blood glucose control to prevent ESRD in patients with T1DM. Among the 988 subjects, with a mean follow-up of 17 years and follow-up rate of 89%, the incidences of ESRD patients in groups D and E who had ≥ 10% HbA1c during the follow-up period, were markedly higher than those in the other three groups (group A: < 8%, group B: 8.0–8.9%, and group C: 9.0–9.9%). Furthermore, Contal and O'Quigley analysis revealed the cut-off point of HbA1c for the onset of ESRD was 10.0%. The cumulative incidence of ESRD in T1DM patients abruptly increased after the persistence of ≥ 10% HbA1c for 15 yr.

Further, as indicated for patients with type 2 diabetes mellitus (T2DM), blood glucose control is closely related to the onset/deterioration of DKD and onset of ESRD in patients with T1DM (2, 10–16). According to the DCCT/EDIC study, the cumulative incidence of kidney disease after a 30-yr duration of diabetes in conventional and intensified therapy groups was 25 and 17%, respectively, suggesting that favorable blood glucose control can improve the reduced glomerular filtration rate (GFR) (13). In addition, we previously reported that HbA1c is a significant risk factor for the onset of ESRD (4).

The impact of long-term glycemic control on the delayed onset of ESRD is supported by Skupien J *et al.* in the Joslin Proteinuria Cohort study (14, 15). They investigated T1DM patients who developed proteinuria between 1990 and 2004 and followed them until 2011 to ascertain the onset of ESRD. Patients in whom post-baseline HbA1c improved beyond the pre-baseline HbA1c had a significantly lower cumulative risk of ESRD after 15 yr than those whose post-baseline HbA1c was average during the first half of follow-up (median, 5.1 yr) and did not improve beyond the pre-baseline HbA1c (29% vs. 42%; P < 0.001). In our study, the cumulative incidences of ESRD after 15 yr of follow-up were 11% in group D and 31% in group E (Fig. 1). We

reviewed the cumulative incidence of ESRD with average HbA1c values in the follow-up period in this study. However, we did not classify patients into the improvement group, no change group, or aggravation group based on HbA1c values. The SD of the average HbA1c during the observation period in groups A–D was 0.3–0.5 (Table 1) and that in group E was high (SD: 1.1). This suggested that the patients in group E had a significant change in HbA1c, and it is possible that this change influenced the onset of ESRD.

There have been some studies on the period from diagnosis until ESRD progression in T1DM. Finne *et al.* (17) reported a crude incidence rate of ESRD. Within 15 yr of the diagnosis of diabetes, ESRD was rare. Thereafter, the incidence rate increased rapidly. Lecaire *et al.* (16) reported that the prevalence of ESRD increased with duration in patients diagnosed from 1960 to 1980 after 15 yr of the disease. Helve *et al.* (3) stated that the incidence of ESRD started to rise 15 yr after the diabetes diagnosis. Furthermore, Gagnum *et al.* (18) found that ESRD developed in only three of 103 ESRD patients before 15 yr after the diagnosis of diabetes, but the incidence significantly increased between 15 and 25 yr after diagnosis. These reports did not demonstrate a connection between glycemic control and ESRD. In this study, we found that ESRD developed in only four of 63 ESRD patients before 15 yr after diagnosis.

Is the cumulative incidence of ESRD related to an elevated HbA1c level lasting several years? In this study, we did not have HbA1c data for an average of 6 yr from baseline. However, we found that 128 patients had ≥ 10% HbA1c (H-HbA1c) during follow-up out of 504 patients with ≥ 10% HbA1c at baseline. We considered these 128 patients to have had persistent H-HbA1c since the time of diagnosis. The cumulative incidence of ESRD abruptly increased after the persistence of H-HbA1c for 15 yr in T1DM patients. This is consistent with a report by Skupien J *et al.* (15) that HbA1c values of around 8–9% may be sufficiently low to avoid ESRD in patients with

T1DM.

However, proteinuria, renal dysfunction, and introduction of dialysis cannot be explained by poor glycemic control alone. The high blood glucose level causes glomerular hyperfiltration, which stimulates mesangial cells to promote the increase in extracellular matrix proteins, thickening of the glomerular basement membrane and charge barrier against albumin, disruption of the size barrier, leakage of albumin urine, and advanced glomerulosclerosis (19). Similarly, the vascular endothelium thickens and hardens, resulting in hypertension. In addition, systemic hypertension exacerbates glomerular hypertension and further advances glomerulosclerosis. Some of these mechanisms have been demonstrated to be genetically susceptible. However, considerably poor glycemic control has a potent effect that determines the introduction of dialysis, which outweighs the effects of other factors.

We reviewed the strengths and weaknesses of this study. The relationship between the cumulative incidence of ESRD and mean HbA1c value during long-term follow-up was analyzed based on observational study design. Risk factors for the onset of ESRD include blood glucose control (4, 20–26), other factors such as blood pressure (4, 17, 18, 20–24), lipids (27), and time-related differences in the level of medical practice (4, 12, 15). Furthermore, the effects of blood glucose level, blood pressure, lipids, and anemia may depend on the stage of kidney disease, and the influence of interventions may differ (27). Subcutaneous injection of erythropoietin in predialysis-stage renal failure is useful for reducing kidney hypofunction (28). We examined the influence of the mean HbA1c value during long-term follow-up, but several intervention strategies were performed with varying effects. In addition, the HbA1c value does not reflect diurnal changes in the blood glucose level, which decreases prior to the onset of ESRD (29). Considering this, we analyzed the relationship between ESRD and HbA1c, which

is a potential limitation. On the other hand, in this study, the mean systolic blood pressure during follow-up was similar to that at the time of registration in groups A to E; therefore, there may have been no confounding effects of blood pressure on the results of analysis based on HbA1c. In group E, the incidence of proteinuria at the time of registration (17.5%) was higher than those in the other groups, suggesting E to be a high-risk group. However, as a background factor, the persistently high HbA1c values before registration in groups D and E may have led to the above finding. Smokers accounted for a high percentage of Group C/D patients and those with high HbA1c values, suggesting poor compliance and the influence of smoking on the onset of ESRD. The merits of this study include long-term follow-up of a large number of patients with T1DM, a high follow-up rate, and the cohort study design. However, despite being a diabetes-specialist institution, 72 (13.4%) of 537 recent patients with diabetes belonged to groups D and E. Thus, we must further improve blood glucose control in the future. There was a 6-yr duration of diabetes between baseline and diagnosis, and the glycemic control state during that period was not clear. As the subjects were followed-up for ≥ 3 yr, HbA1c was not continuously measured for 17 yr. We used the average HbA1c value during the observation period as an index of glycemic control in this study. HbA1 measurement started in 1980, and the glycemic control situation at that time is unclear. The mean number of measurements of HbA1c in the observation period was 115 ± 78 (mean $\pm$ SD).

In conclusion, according to the Contal and O'Quigley analysis, the cut-off point for HbA1c predicting a higher risk of ESRD was 10.0% in Japanese patients with T1DM. HbA1c values of ≥ 10% lasting for 15 yr were associated with a high risk of ESRD.

Whether maintaining the mean HbA1c value below this value is effective for the prevention of ESRD in patients with T1DM needs to be clarified in future prospective studies. We must

manage HbA1c so that it does not exceed 10% in order to prevent ESRD.

Conflict of interest: The authors declare that they have no conflict of interest.

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