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ORIGINAL ARTICLE

Clinical background of Japanese patients with type 1 diabetes mellitus who have received insulin therapy for 50 years or longer

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Abstract

Aims We clarified the clinical background of Japanese patients with type 1 diabetes mellitus (T1DM) who have received insulin therapy for 50 years or longer.

Methods Of 1,412 patients diagnosed with T1DM at an age younger than 30 years old between 1962 and 2000, 29 had a 50-year or longer history of diabetes. We investigated the mean values of HbA1c and systolic blood pressure (SBP) during follow-up, as well as diabetic retinopathy, diabetic nephropathy, and macroangiopathy.

Results The mean age of the subjects at the time of diagnosis was 10 years and that at the completion of this survey was 66 years. The mean follow-up period was 43 years. The mean HbA1c value and SBP during the follow-up period were 8.2% and 130 mmHg, respectively. Seventeen percent of patients did not have diabetic retinopathy, 59% had proliferative retinopathy, and 66% had undergone photocoagulation. Fifty-four percent of patients did not have microalbuminuria and 11% had end-stage renal disease. Macroangiopathy was observed in 46%, cardiovascular disease (CVD) in 25%, and ischemic stroke in 18%.

Conclusions It became possible for patients with T1DM to live more than 50 years in Japan.

Keywords Type 1 diabetes mellitus · Diabetic retinopathy · Diabetic kidney disease · Macroangiopathy

Introduction

In the latter half of the 1950s in Japan, insulin became commercially available, and T1DM was recognized as a disease with achievable survival. Niimi [1] reported that the number of patients with childhood-onset T1DM in Japan before 1954 was approximately 100. In Japan, there had been no case report of survival in T1DM patients before 1952. Thereafter, improvement in insulin therapy was promoted, as described below. In the 1950s, once-a-day injection of protamine zinc insulin or NPH preparations was introduced. In the 1960s, bovine/porcine insulin preparations became commercially available. In 1963, a summer camp for childhood diabetes was started. In the mid-1970s, once-a-day injection was switched to twice-a-day injection. In 1976, a pilot study for blood glucose self-monitoring was initiated. In 1980, HbA1 measurement was started in our center. In 1981, the self-injection of insulin became covered by health insurance, and HbA1c measurement was started in 1983. In 1986, human insulin preparations became commercially available, and blood glucose self-monitoring became covered by health insurance. In addition, the DCCT study was published in 1993, emphasizing the importance of strict blood glucose control [2].

In the "Joslin 50-year Medalist Study" [3], proliferative diabetic retinopathy (PDR) was absent in 49%, microalbuminuria was not present in 70%, and cardiovascular disease (CVD) was noted in 48%. There are no reports of diabetic microangiopathy or macroangiopathy in patients with T1DM with a duration of diabetes of 50 years or longer in Japan.

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In this study, we clarified the clinical background of Japanese patients with T1DM who received insulin therapy for 50 years or longer.

Subjects and methods

Patient recruitment

Of 1,412 Japanese patients with T1DM who consulted Tokyo Women's Medical University School of Medicine for the first time between 1962 and 2000 (December 31), there were 29 subjects with a 50-year or longer history of diabetes (as of December 31, 2015, or until death) (8 males, 21 females). We investigated the mean HbA1c value during follow-up from 1983 or on the initial visit, mean systolic blood pressure at the outpatient clinic, and state of diabetic retinopathy/diabetic nephropathy/macroangiopathy in 2015.

A diagnosis of T1DM was made according to the classification of diabetes and diagnostic criteria established by the Japan Diabetes Society (JDS) [4, 5]. After serum C-peptide and anti-glutamic acid decarboxylase (GAD) antibody tests became possible, the disease type was classified based on the results; however, we excluded patients who had not required insulin therapy for a few years despite GAD antibody-positive reactions for clinical reasons.

Measurements

The level of glycohemoglobin was measured by high-performance liquid chromatography (HPLC; A8120, HA8121, HA8131, HA8150, HA8160, HA8180: ARKRAY, Kyoto, Japan) from 1983. The hemoglobin A1c (HbA1c) value was converted to the NGSP value [6] (as %). The systolic blood pressure was measured after resting for 5 min or longer at the outpatient clinic on consultation. The annual mean values of HbA1c and systolic blood pressure were calculated, and the mean values during the follow-up period were calculated.

Complications

Diabetic retinopathy was diagnosed by ophthalmologists by dilated pupils. The first day of photocoagulation was investigated based on medical records. Diabetic retinopathy was classified into 4 groups: no apparent retinopathy, no proliferative retinopathy, proliferative retinopathy, and ungradable. The state of diabetic nephropathy was evaluated based on the urinary albumin-to-creatinine ratios (ACRS) measured at least twice in 2015. Diabetic nephropathy was classified into 5 stages: stage 1, normoalubuminuria (mg/g Cr) (< 30) and eGFR (mL/min/1.13 m^2) ≥ 30; stage 2, microalbuminuria (30–299) and eGFR ≥ 30; stage 3, macroalbuminuria (≥ 300) or persistent proteinuria (≥ 0.5 g/g Cr) and eGFR ≥ 30; stage 4, any albuminuria/proteinuria status and eGFR < 30; and stage 5, any status on continued dialysis therapy [7]. The diabetes follow-up period was calculated as the interval from registration (initial visit) until the date of stage 5, death, final visit, or survey completion (December 31, 2015). Macroangiopathy was classified into 4 diseases (CVD, ischemic stroke, peripheral artery disease [PAD], and occlusion or stenosis of the internal carotid artery). Based on medical records, we investigated the presence or absence of therapy with renin–angiotensin–system inhibitors (RASI) or statins at the time of registration or during the follow-up period and smoking/cancer during follow-up, as well as other diseases.

Statistical analysis

The data are expressed as the mean ± SD. In patients with events (stage 5 or death), the follow-up period was regarded as the interval from registration until the date of event appearance. In those without events, it was regarded as the interval from registration until completion of the follow-up survey (December 31, 2015). In those who discontinued consulting the outpatient clinic in the absence of stage 5, the follow-up period was calculated as the interval from registration until the final visit. Furthermore, the cumulative rate of patients who had undergone photocoagulation was analyzed using the Kaplan–Meier method with the follow-up period and duration of diabetes. We used JMP Pro software (Ver. 12.1, Windows, SAS Institute, Inc, Cary, NC).

Results

Clinical characteristics of the subjects and management of diabetes

As the subjects, 29 patients (8 males, 21 females) were extracted. Their clinical characteristics are shown in Table 1. The mean age at onset was 10 years. That at the completion of this survey was 66 years (male: 66 years, female: 65 years). The mean duration of diabetes was 55 years, and the mean follow-up period was 43 years (median: 48 years). The mean heights of the males and females were 158 ± 7 and 152 ± 6 cm, respectively. The height of 1 male (170 cm) exceeded the mean height of males of the same age group (mean height of Japanese aged 60–69 years: male, 166 cm; female, 153 cm) [8]. Four patients had a body mass index (BMI) of ≥ 30 kg/m^2 in 2015. In 1 male, it exceeded 35 kg/m^2. The mean dose of insulin in 2015 was 37.8 ± 19.9 units/day (0.6 ± 0.2 units/kg/day). In 74% of the patients, insulin injection was performed 4 times a day or more. The frequency of injection was 3 times a day in 19% and twice a day in 7%.

Table 1 Clinical characteristics of patients with type 1 diabetes for 50 years or longer

Baseline characteristics ($n=29$)			
Age (years)	65.5 ± 7.3	[54.4–86.0]	(29)
Age at diagnosis (years)	10.1 ± 6.5	[1.5–27.9]	(29)
Age at baseline (years)	23.0 ± 11.4	[5.9–45.4]	(29)
Duration of diabetes (years)	55.4 ± 3.9	[50.2–64.9]	(29)
Year of follow-up (years)	42.5 ± 9.5	[20.3–53.9]	(29)
Sex: male (%)	27.6		(8)
Smoking history (%)	24.1		(7)
History of hypertension (%)	69.0		(20)
ARB and/or ACE-I use (%)	69.0		(20)
Statin use (%)	48.3		(14)
Weight (kg)	57.2 ± 12.3	[38.2–87.0]	(27)
Height (cm)	153.5 ± 6.9	[143.0–169.7]	(29)
BMI (kg/m^2)	24.3 ± 4.5	[18.2–36.2]	(27)
Insulin dose (unit/kg/day)	0.6 ± 0.2	[0.3–1.2]	(26)
Current HbA1c (%)	7.6 ± 1.0	[6.2–9.6]	(22)
Longitudinal HbA1c (%)	8.2 ± 0.8	[6.8–10.1]	(28)
Current systolic BP (mmHg)	131.1 ± 12.6	[109–163]	(22)
Longitudinal systolic BP (mmHg)	129.4 ± 8.7	[113–146]	(28)
Serum creatinine (mg/mL)	0.8 ± 0.2	[0.4–1.2]	(25)
Albumin creatinine ratio (mg/g Cr)	271.8 ± 1068.9	[2.7–5380]	(26)
eGFR (mL/min./1.73m2)	63.3 ± 15.2	[35.4–85.5]	(25)
HDL (mg/dL)	72.7 ± 17.5	[53–128]	(25)
LDL (mg/dL)	105.2 ± 21.9	[70–165]	(25)
Triglycerides (mg/dL)	109.8 ± 65.6	[36–305]	(25)
C-peptide > 0.4 ng/mL (%)	6.9		(2)

Data are mean ± SD [range] (n) or % (n)

The mean HbA1c value (NGSP) during the follow-up period from 1983 or on initial consultation was 8.2% (Table 1). The changes in the annual mean of HbA1c in individual T1DM patients are shown in Fig. 1a. The HbA1c value increased until 1990 and decreased after 1990.

The mean systolic blood pressure measured on consultation at the outpatient clinic during the follow-up period from the initial consultation was 130 mmHg (Table 1). Concerning the changes in the annual mean of systolic blood pressure, the systolic blood pressure increased until 2000, but reached a plateau or decreased after 2000 (Fig. 1b). Of the 29 patients, 20 (69%) received angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACE-Is), or both (Table 1).

With respect to serum lipids in 2015, the high-density lipoprotein (HDL), low-density lipoprotein (LDL), and neutral fat levels were 73, 105, and 110 mg/dL, respectively, demonstrating favorable control. Of the 29 patients, 14 (48%) received statins (Table 1).

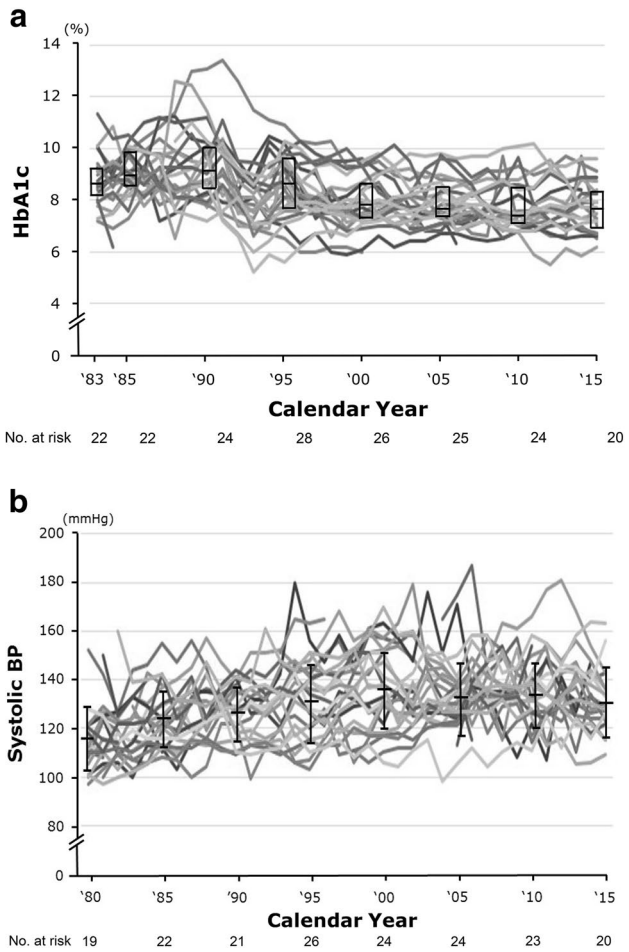

Fig. 1 Annual mean values of HbA1c (**a**) and systolic blood pressure (**b**) during follow-up in patients with T1DM who received insulin therapy for 50 years or longer. The data **a** are expressed as the median and IQR, and the data **b** are expressed as the mean and SD

Diabetic complications

At the final point of observation, diabetic retinopathy was absent in 5 patients (17%), and proliferative retinopathy was present in 17 (59%) (Fig. 2). Photocoagulation had been performed in 19 (66%). Two patients (7%) had lost their eyesight on the bilateral sides, and 2 (7%) on the unilateral side. The cumulative rate of patients treated by photocoagulation began to increase in patients with a disease duration of ≥ 15 years, reaching a plateau in those with a disease duration of ≥ 35 years (Fig. 3a). Furthermore, the cumulative rate of patients treated by photocoagulation began to increase in patients with an age of ≥ 23 years, reaching a plateau in those with an age of ≥ 50 years (Fig. 3b).

Of 28 patients in whom the assessment of diabetic nephropathy was possible at the final point of observation, stage 1 was absent in 15 (54%), stage 2 was present in 7 (25%), stage 3 in 3 (11%), and stage 5 in 3 (11%) (Fig. 2).

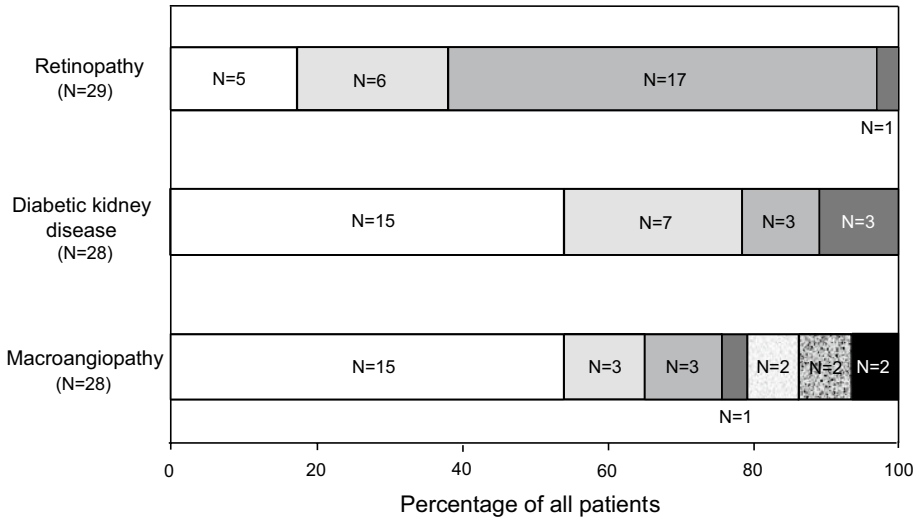

Fig. 2 Prevalence of diabetic micro- and macroangiopathy in 2015 in patients with T1DM who received insulin therapy for 50 years or longer. Diabetic retinopathy: □, no apparent retinopathy; ▨, no proliferative retinopathy; ▩, proliferative retinopathy; ■, ungradable. Diabetic nephropathy: □, stage 1; ▨, stage 2; ▩, stage 3; ■, stage 5. Macroangiopathy: □, no macroangiopathy; ▨, cardiovascular disease (CVD); ▩, ischemic stroke (IS); ■, peripheral artery disease (PAD); ▨, occlusion or stenosis of the internal carotid artery; ▩, CVD + IS; ■, CVD + PAD

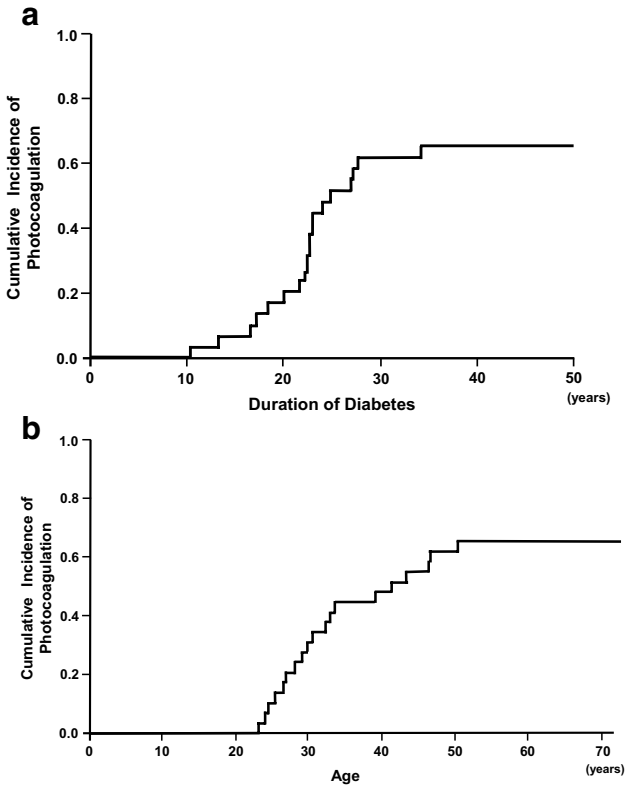

Fig. 3 Cumulative rate of patients treated by photocoagulation (Kaplan–Meier method). The duration of diabetes (**a**) and the age (**b**) was regarded as the interval until event appearance

In addition, mean HbA1c value for the past 29 years in the patients more than stage 2 was 8.3% (vs. stage 1; 8.0%, $P = \text{NS}$).

Macroangiopathy was observed in 13 (46%) of the 28 patients: CVD in 7 (25%), ischemic stroke in 5 (18%), PAD in 3 (11%), and occlusion/stenosis of the internal carotid artery in 2 (7%) (Fig. 2).

Seven patients (24%) had cancer: breast cancer in 2 (7%), kidney cancer in 2 (7%), liver cancer in 1 (3%), esophageal cancer in 1 (3%), and duodenal/esophageal cancer in 1 (3%).

Other diseases and mortality

Nine patients (31%) had autoimmune diseases. Of these, 7 (24%) had autoimmune thyroid disease, 1 (3%) had collagen disease, and 1 (3%) had rheumatoid arthritis. Furthermore, 20 patients (69%) had hypertension and 14 (48%) had dyslipidemia.

In this cohort, 4 patients died: 2 died of pneumonia and 2 of cancer (3 males, 1 female; mean age at the time of death: 74 years).

Discussion

In this study, we investigated the profiles of patients with a 50-year or longer history of T1DM, for whom insulin therapy had been introduced. Of these, 66% underwent photocoagulation. The prevalence of diabetic nephropathy and CVD was 46% and 25%, respectively.

Concerning the prognosis of T1DM patients, the Diabetes Epidemiology Research International (DERI) Mortality Study compared the mortality rate of Japanese patients who developed T1DM at an age of < 18 years with that of those of the same age group [9, 10]. The standardized mortality ratio (SMR) in the 1965–69 onset group ($n = 281$) among Japanese patients with T1DM (Japan DERI cohort, $n = 1{,}408$) was 15.7-times higher than in 1995, but it was 6.9-times higher in the 1975–79 onset group ($n = 769$) [11]. Thus, the prognosis of Japanese patients with T1DM has rapidly

improved, being similar to those in Europe and the United States. Furthermore, we divided 1,054 Japanese patients diagnosed with T1DM at an age of < 30 years from 1962 until December 31, 1999, into 3 groups based on the year of onset: before 1979 (group A), 1980s (group B), and 1990s (group C), and analyzed the life table, and calculated the mortality rate (/100,000 person-years) and SMR [12]. The values (95% CI) in groups A, B, and C were 574 (419–728) and 1.1 (0.8–1.4), 242 (133–351) and 1.5 (0.8–2.1), and 143 (29–257) and 1.5 (0.2–2.7), respectively. In addition, the cumulative survival rate in recently diagnosed T1DM patients was markedly high ($P = 0.0128$).

We have the limitations in this study. (1) There are few subjects at 29. (2) The start of measurement of HbA1c was from 1983 in the Diabetes Center of Tokyo Women's Medical Hospital. In our subjects, T1DM was diagnosed before 1965. The glycemic control state was not clear until 1983.

We compared blood glucose control and diabetic complications among the Joslin 50-year medalist study, the Golden Years cohort in Diabetes UK, and this study [3, 13, 14] (Table 2). With respect to long-term blood glucose control, HbA1c was measured from 1993 in the "Joslin 50-year Medalist Study", and the longitudinal and current HbA1c values were 7.7% and 7.3%, respectively, in 73 medalists (20.3%) (mean frequency of measurement: 20.4 times) [3]. Furthermore, a cross-sectional survey involving Diabetes UK award medalists demonstrated that the HbA1c value was 7.6% [13]. In our survey, the longitudinal and current HbA1c values were 8.2% (mean frequency of measurement: 236.1 times) and 7.6%, respectively, being similar to those in the United States and the United Kingdom.

Concerning diabetic retinopathy, proliferative diabetic retinopathy (PDR) was absent in 49% of the patients in the "Joslin 50-year Medalist Study" [3]. On the other hand, the survey involving Diabetes UK award medalists indicated that severe diabetic retinopathy was commonly observed, and that 43% of patients had undergone photocoagulation [13]. In this study, PDR was not present in 38% of patients and 66% had undergone photocoagulation. Thus, in this study, severe retinopathy was frequently observed; poor blood glucose control may have persisted over a long period under an inadequate medical environment during adolescence. The incidence of proliferative retinopathy in T1DM patients diagnosed between 1960 and 69 in the Wisconsin Epidemiologic Study was 20% by 15 years of diabetes duration [15]. However, the incidence of photocoagulation increased rapidly from 15 years of diabetes duration in this study, and reached a plateau after 35 years. A high incidence of severe retinopathy was found in this study, but it is thought to be due to an inadequate medical environment in which hyperglycemia/hypoglycemia was repeated on an insulin regimen of once-a-day during adolescence.

Concerning diabetic nephropathy, microalbuminuria was not present in 70% of patients in the "Joslin 50-year Medalist Study" [3]. Furthermore, the survey involving Diabetes UK award medalists indicated that 64% of patients were normoalbuminic [14]. However, 54% of patients were normoalbuminuric in this study; showing a marked difference. In addition, the mean HbA1c value for the past 29 years in the patients more than stage 2 was 8.3% in this study.

With respect to macroangiopathy, CVD was noted in 48% of patients in the "Joslin 50-year Medalist Study" [3]. Furthermore, the survey involving Diabetes UK award medalists indicated that CVD was present in 34% of patients [13]. In this study, its prevalence was 25%. Furthermore, ischemic stroke was observed in 18% in this study. Thus, there was a difference in the prevalence of CVD between Europe/the United States and Japan [16–18], as demonstrated for type 2 diabetes mellitus. Although glycemic control was poor, the incidence of CVD was low in this study, and the association of a factor except blood glucose level and the influence of racial

Table 2 Comparison of blood glucose control and diabetic complications among Joslin 50-years medalists, Diabetes UK medalists, and this study

	Joslin 50-year medalists [3] ($n = 351$)	Diabetes UK medalists [13, 14] ($n = 400$)	Current study ($n = 29$)
Hemoglobin A1c (HbA1c)			
Longitudinal HbA1c	7.7% ($n = 73$) [1993–2007]		8.2% ($n = 28$) [Initial visit (1983)–2015]
Current HbA1c	7.3% ($n = 342$) [2007]	7.6% [1993–1996]	7.6% ($n = 22$) [2015]
Diabetic retinopathy			
No proliferative diabetic retinopathy	49%		38%
Proliferative diabetic retinopathy		Common	59%
Photocoagulation		43%	66%
Diabetic nephropathy	30%	36%	46%
Macroangiopathy			
Cardiovascular disease	48%	34%	25%

differences were suggested. In addition, there were 20 patients (69%) with a history of hypertension in our diabetes center, all of whom took ARB or ACE-I. In contrast, the number of patients with a history of hypertension was 56% in the "Joslin 50-year Medalist Study" [3], and ACE-I internal use was 40%, showing a difference between Joslin's study and our study. However, 14 patients (48%) took statin in our center, and 65% took it in Joslin's study [3].

With respect to the relationship between blood glucose control and diabetic complications, according to the DCCT/EDIC study report in 2009, the subjects were assigned to receive standard insulin therapy (previous standard insulin therapy group) [once- to twice-a-day insulin therapy] or intensified insulin therapy (previous intensified–intensified insulin therapy group) [a normal blood glucose level was targeted by 3 times a day or frequent insulin/pump therapies] in the DCCT study from 1983 until 1993. In the DCCT study from 1993, intensified insulin therapy was performed for all patients, and the incidence of diabetic complications was compared with that in the EDIC observational study [19]. In the previous standard insulin therapy group (DCCT study), the cumulative incidences of proliferative retinopathy, diabetic nephropathy, and CVD 30 years after the onset of diabetes mellitus were 50, 25, and 14%, respectively. In the EDIC cohort, they were 47, 17, and 14%, respectively. However, in the previous intensified–intensified insulin therapy group (DCCT study), the percentages were 21, 9, and 9%, respectively, showing decreases in the cumulative incidences. In 2016, two articles were published from the DCCT/EDIC studies. A sub-analysis of cardiovascular disease 30 years after the start of intervention revealed that intensified insulin therapy in the 1st decade decreased the incidence of cardiovascular disease 30 years after the start of intervention by 30% [20]. When comparing the mortality rate between patients participating in the DCCT/EDIC studies and the general population in the United States, there was no difference in the mortality rate between T1DM patients and the general population [21]. The state of glycemic control in our country has finally caught up with that in Europe and America, and future improvement is anticipated regarding the diabetic complication and mortality rate.

In Japan, insulin therapy for T1DM was recently introduced in line with Europe and the United States. This is the first report on this therapy. Since 1980, the environment for insulin therapy has rapidly been improved, facilitating more favorable blood glucose control (Fig. 1a). At last it became possible for the patients with T1DM to live more than 50 years in Japan.

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Compliance with ethical standards

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

Ethical policy All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later version. Informed consent or a substitute for it was obtained from all patients included in the study. This study obtained the approval of the Tokyo Women's Medical College Ethical Review Board (Approval date: Jan 16, 2017, No. 4,233).

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