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ORIGINAL ARTICLE

Impact of treatment cessation on incidence and progression of retinopathy in Japanese patients with type 2 diabetes mellitus: a retrospective cohort study

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Abstract

Aims This cohort study investigated the association between treatment cessation and incidence/progression of diabetic retinopathy (DR) in Japanese patients with type 2 diabetes mellitus (T2DM).

Materials and methods Data were extracted from electronic medical records at the University of the Ryukyu Hospital and the Tomishiro Central Hospital of Okinawa, Japan. We enrolled 417 diabetic patients without DR ($N=281$) and with nonproliferative DR ($N=136$) at the baseline. Treatment cessation was defined as failing to attend outpatient clinics for at least twelve months prior to the baseline. After a median follow-up of 7 years, we compared the incidence/progression rate of DR including nonproliferative and proliferative DR between patients with and without treatment cessation and calculated the odds ratio (OR) in the treatment cessation group using a logistic regression model.

Results The overall prevalence of treatment cessation was 13% in patients with T2DM. Characteristics of treatment cessation included relative youth (57 ± 11 years vs. 63 ± 12 years, $P<0.01$). Treatment cessation was tightly associated with the incidence of DR (OR 4.20 [95% confidence interval [CI] 1.46–12.04, $P<0.01$) and also incidence/progression of DR (OR 2.70 [1.28–5.69], $P<0.01$), even after adjusting for age, sex, BMI, duration of T2DM, and HbA1c level.

Conclusions By considering major confounding factors, the present study demonstrates an independent association between treatment cessation and incidence of DR in patients with T2DM, highlighting treatment cessation as an independent risk for DR in T2DM.

Keywords Treatment cessation · Type 2 diabetes mellitus · Diabetic retinopathy · Incidence and progression · Retrospective cohort study

Introduction

It has been well-documented that risk factors for the incidence of diabetic retinopathy (DR) include chronic hyperglycemia, disease duration, hypertension, dyslipidemia, and diabetic nephropathy [1–3]. In a large-scale of observational study consisting of approximately 20,000 patients with type 2 diabetes mellitus (T2DM) without proliferative diabetic retinopathy (PDR) in the UK, the baseline rate of patients without DR (NDR) was 79% and nonproliferative retinopathy (NPDR) was 21% [4]. After 5 years, only a few patients without retinopathy at the baseline developed NPDR (cumulative incidence 4%) and PDR (0.7%), and after 10 years, the respective cumulative incidences were 16% for NPDR and 1.5% for PDR. Among those with NPDR at the baseline, after 1 year, 6% developed PDR, and after 10 years, the cumulative incidence was 11% [4].

The 2022 American Diabetes Association and the European Association for the Study of Diabetes consensus report on T2DM care highlights that reducing treatment cessation is critical for therapeutic strategies [5]. As evidenced by meta-analyses [6–8], characteristics of patients with treatment cessation [9–12], relationships between

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cessation and major clinical parameters [13–15], reasons for cessation [16–19], and also evaluation of interventions on patients with cessation [20–25] have been widely recognized. To date, patients with treatment cessation have been characterized by relative youth, smoking habit, obesity, and poor glycemic control [13]. To our surprise, however, there are limited reports investigating the association between treatment cessation and diabetic complications in diabetic patients. In a baseline observation of a large cohort study investigating treatment cessation and all-cause mortality in 15,000 patients with T2DM receiving insulin in the UK, the prevalence of macroangiopathy was comparable between treatment cessation and nontreatment cessation groups [26]. However, the prevalence of DR or nephropathy was higher in patients with treatment cessation as compared to nontreatment cessation [26]. Although a cohort study reported that treatment cessation was associated with the subsequent occurrence of DR in patients with T2DM [27], confounding factors including HbA1c level and duration of T2DM were not taken into account in this report. Based on these backgrounds, we investigated whether treatment cessation in patients with T2DM would increase the risk of incidence and progression of DR, using preexisting medical records of hospitals in Okinawa, Japan.

Materials and methods

Study design and subjects

The present study was approved by the institutional ethical committee of the University of the Ryukyus for Medical and Health Research Involving Human Subjects (No.765) on February 27, 2015, and was conducted in accordance with the Declaration of Helsinki. This study was a retrospective cohort study, and data were obtained from electronic medical records at two hospitals in Okinawa, Japan. We enrolled 975 patients with T2DM either at the University of the Ryukyu Hospital or the Department of Diabetes and Life-Style Related Disease Center, Tomishiro Central Hospital, from January to December in 2009. Based on the results at the first fundus examination in 2009 and the first blood sampling examination in 2009, in about 70% of cases, both fundus examination and blood sampling were done on the same day, but in about 30% of cases, there was a time point difference ranging from 1 to 3 months. Among those 975 patients, 157 subjects with proliferative DR were excluded, and also 401 subjects who had failed to attend ophthalmologist appointments or were only followed up for less than 4 years were excluded. Consequently, a total of 417 subjects were eligible for analyses (Fig. 1).

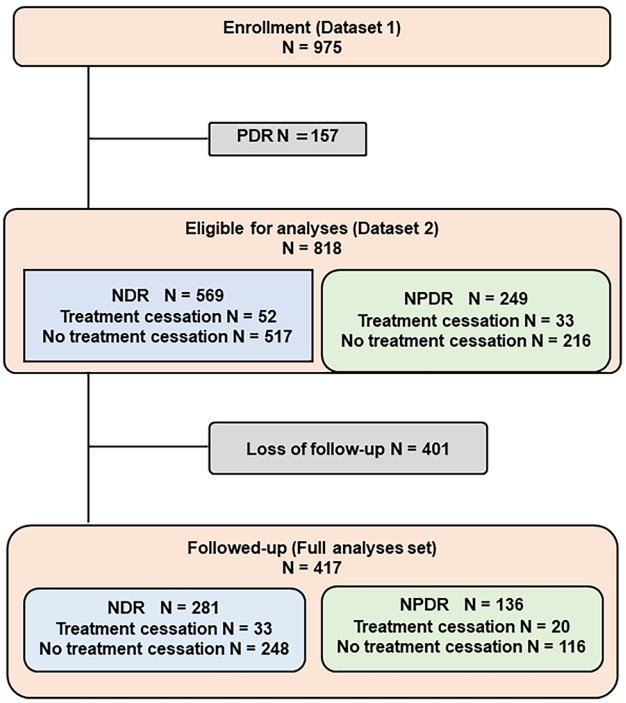

Fig. 1 Research design. We enrolled 975 patients with type 2 diabetes mellitus (T2DM) from January to December in 2009 (Dataset 1). After 157 patients of PDR were excluded, 818 patients either with NDR ($N=569$) or NPDR ($N=249$) were included (Dataset 2). The full analysis set included 417 patients after the exclusion of patients without follow-up (Dataset 3). *NDR* no diabetic retinopathy, *NPDR* nonproliferative diabetic retinopathy; and *PDR* proliferative diabetic retinopathy

Assessment of treatment cessation

Treatment cessation of patients was defined as failing to attend T2DM outpatient appointments for at least twelve months prior to the baseline [28].

Assessment of incidence and progression of DR

The severity of DR was determined at the baseline and after the follow-up, by qualified ophthalmologists at either the University of the Ryukyu Hospital or the Tomishiro Central Hospital. According to the modified international clinical DR severity scales [29], we classified subjects into the following three groups: no diabetic retinopathy (NDR), nonproliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). In the case where the severity of the right or left eyes was different, the eye condition was taken for more severe staging. Incidence and progression of DR were assessed in diabetic subjects with either NDR or NPDR at the baseline from a series of

examinations from 2009 to 2013 or later (i.e., from NDR to NPDR or PDR or from NPDR to PDR). Incidence of DR was assessed in diabetic subjects with NDR at the baseline by worsening in stage (i.e., from NDR to NPDR or PDR), and progression of DR in diabetic subjects with NPDR at the baseline was defined as a worsening in stage (i.e., from NPDR to PDR) [30, 31].

Assessment of other factors

Serum biochemical variables were measured by conventional automated analyzers. Dyslipidemia was identified by the current use of anti-dyslipidemic drugs. Overt proteinuria was defined as positive in case the result showed ±, 1+, 2+, 3+, and 4+, as measured by semi-qualitative urinary protein stick test after two consecutive months. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2).

Statistical analyses

Initially, baseline clinical characteristics for the no treatment cessation and treatment cessation groups were shown as means (with their standard deviations (SDs)) for continuous variables with a normal distribution, medians (25%, 75%) for continuous variables with a non-normal distribution, and the number of subjects (*n*) (%) for categorical variables. The characteristics were then compared between the groups of treatment cessation status using unpaired *t*-tests for continuous variables with a normal distribution, Kruskal–Wallis test for continuous variables with a non-normal distribution, and chi-square test for categorical variables.

Next, to compare the incidence of DR between T2DM patients of NDR at the baseline with and without treatment cessation, a logistic regression model was used to calculate the odds ratio (OR) (95% confidence interval [CI]) for incidence of DR in the treatment cessation group with the no treatment cessation group serving as the reference after adjusting for age (years as a continuous variable), sex (male or female as a categorical variable), BMI (kg/m^2 as a continuous variable), duration of T2DM (years as a continuous variable), and HbA1c level (% as a continuous variable). In addition, to compare the progression of DR between T2DM patients of NPDR at the baseline with and without treatment cessation, a logistic regression model was used to calculate the OR (95% CI) for the progression of DR in the treatment cessation group after adjusting for possible confounding factors in the same fashion. Furthermore, to compare the incidence/progression of DR between T2DM patients with either NDR or NPDR at the baseline with and without treatment cessation, a logistic regression model was used to calculate the OR (95% CI) for incidence/progression of DR in the treatment cessation group after adjusting for possible confounding factors in the same fashion. Finally, we calculated all ORs (95% CIs) for all covariates in these multiple logistic regression models.

Statistical analyses were performed using a standard software package (JMP version 12; SAS Institute Inc., Cary, NC) unless otherwise indicated. All probability values were two-tailed, and the significance level was set at $P < 0.05$.

Results

Baseline clinical characteristics of study subjects

Clinical characteristics of the cohort at the baseline ($N = 417$) are shown in Table 1. The proportion of men was 56%, the mean age was 62 ± 12 years, and the mean BMI was 25.4 ± 4.4 kg/m^2. The average level of HbA1c at the baseline was 7.7 ± 1.6%. The median duration of T2DM was 10 (5, 16) years. The prevalence of treatment cessation in all patients was 13%. As compared to the no treatment cessation group, the treatment cessation group were relative youth in age (57 ± 11 years vs. 63 ± 12 years, $P < 0.01$). The treatment cessation group also showed a higher HbA1c level than the group without treatment cessation, although the difference was not statistically significant.

Rate of incidence of DR and its OR

The incidence rate of DR was 25% ($N = 69$, NPDR; $N = 65$, PDR; $N = 4$) among T2DM patients with NDR at the baseline ($N = 281$) over a follow-up with a median of 7 years (Fig. 2). As shown in Table 2, the incidence rate of DR among patients with treatment cessation was prominently higher at 58% as compared to incidence rate of DR in patients without treatment cessation (20%). In logistic regression analyses, the OR for incidence of DR in the treatment cessation group, with the no treatment cessation group serving as the reference, was 5.71 (95% CI 2.59–12.57, $P < 0.01$) after adjusting age and sex and was 4.20 (95% CI 1.46–12.04, $P < 0.01$) after further adjusting BMI, duration of T2DM, and HbA1c level (Table 2 and Supplemental Table 1). In addition, higher HbA1c was also significantly associated with the incidence of DR (OR 1.50 [1.22–1.84] per + 1%, $P < 0.01$) (Supplemental Table 1).

Rate of progression of DR and its OR

The progression rate of DR was 30% ($N = 41$) in T2DM patients with NPDR at the baseline ($N = 136$) (Fig. 2). As shown in Table 3, the progression rate of DR in patients with treatment cessation was apparently higher at 40% as compared to progression rate of DR in patients without treatment cessation (28%). The age and sex-adjusted OR for the

Table 1 Baseline clinical characteristics of study subjects

	All	Treatment cessation	No treatment cessation	*P*
Number (%)	417	53/417 (13)	364/417(87)	
Men (%)	233/417 (56)	33/53 (62)	200/364 (55)	0.32
Age (year)	62 ± 12	57 ± 11	63 ± 12	< 0.01
BMI (kg/m^2)	25.4 ± 4.4	25.5 ± 4.2	25.4 ± 4.4	0.83
Duration of T2DM (years)	10 (5, 16)	10 (5, 18)	10 (5, 16)	0.82
Anti-hypertensive drugs (%)	272/417 (65)	30/53 (57)	242/364 (66)	0.16
Dyslipidemia (%)	296/417 (71)	40/53 (75)	256/364 (70)	0.44
Overt proteinuria (%)	164/365 (45)	22/47 (47)	142/318 (45)	0.78
Diabetic retinopathy (%)	136 /417 (33)	20/53 (38)	116/364 (32)	0.39
Diabetic nephropathy (%)	190/352 (54)	26/42 (62)	164/310 (53)	0.27
History of smoking (%)	160/417 (38)	24/53 (45)	136/364 (37)	0.27
Family history of diabetes (%)	123/417 (29)	14/53 (26)	109/364 (30)	0.60
HbA1c(%)	7.7 ± 1.6	8.0 ± 1.5	7.6 ± 1.6	0.20
ALB (mg/dL)	4.0 ± 0.5	4.0 ± 0.4	4.1 ± 0.5	0.54
Blood urea nitrogen (mg/dL)	17.3 ± 10	18.1 ± 17	17.2 ± 9.0	0.57
Creatinine (mg/dL)	1.0 ± 1.1	1.0 ± 1.0	1.0 ± 1.1	0.90
eGFR (mL/min/1.73 m^2)	67 (40, 85)	74 (28, 89)	67 (42, 84)	0.91
UA (mg/dL)	5.5 ± 1.5	5.4 ± 1.6	5.5 ± 1.5	0.53
Triglyceride (mg/dL)	129 (84, 180)	137 (80, 219)	126 (84, 177)	0.32
LDL-C (mg/dL)	106 ± 38	112 ± 49	105 ± 36	0.41
HDL-C (mg/dL)	51 ± 14	48 ± 11	52 ± 15	0.06
AST (IU/L)	21 (16, 26)	17 (14, 25)	21 (17, 26)	0.11
ALT (IU/L)	21 (15, 31)	19 (13, 30)	21 (15, 31)	0.30
γGTP (IU/L)	26 (17, 46)	32 (17, 53)	26 (17, 45)	0.91

Date are expressed as mean (SD), median [IQR], and *n* (%). Dyslipidemia means use of anti-dyslipidemia drugs, Overt proteinuria means positive of urinary qualitative at two consecutive follow-up months

BMI body mass index, *HbA1c* glycated hemoglobin, *ALB* albumin, *eGFR* estimated glomerular filtration, *UA* uric acid, *LDL-C* low- density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *AST* alanine aminotransferase, *ALT* aspartate aminotransferase, *γGTP* γ-glutamyltransferase.

P values were calculated by one-way ANOVA

progression of DR in the group with treatment cessation was 1.64 (95% CI 0.61–4.41, $P = 0.32$), and the multivariate-adjusted OR was 1.72 (95% CI 0.56–5.34, $P = 0.35$) (Table 3 and Supplemental Table 2). There was no significant determinant associated with progression of DR (Supplemental Table 2).

Rate of incidence and progression of DR and its OR

The incidence and progression rate of DR was 26% ($N = 110$) in T2DM patients with either NDR or NPDR at the baseline ($N = 417$) (Fig. 2). As shown in Table 4, the incidence and progression rate of DR in patients with treatment cessation was prominently higher at 51% as compared to progression rate of DR in patients without treatment cessation (23%). The age and sex-adjusted OR for incidence/progression of DR in the treatment cessation group was 3.48 (95% CI 1.91–6.35, $P < 0.01$), and the multivariate-adjusted OR was 2.70 (95% CI 1.28–5.69, $P < 0.01$) (Table 4 and Supplemental Table 3). In addition, duration of T2DM (OR 1.04 [1.00–1.07] per + 1 year, $P = 0.03$) and higher level of HbA1c (OR 1.39 [1.19–1.62] per + 1%, $P < 0.01$) were also significantly associated with the incidence and progression of DR (Supplemental Table 3).

Discussion

The present cohort study demonstrated that treatment cessation was tightly associated with the incidence of DR in Japanese T2DM patients without DR, independently of major clinical parameters including HbA1c level and duration of T2DM. Treatment cessation was also independently associated with the incidence/progression of DR in T2DM patients with either NDR or NPDR.

In a cross-sectional observation of 15,000 patients with T2DM in the UK, Currie et al. reported that patients with treatment cessation showed a higher prevalence of DR and nephropathy as compared to patients with non-cessation, while the incidence of macroangiopathy was comparable

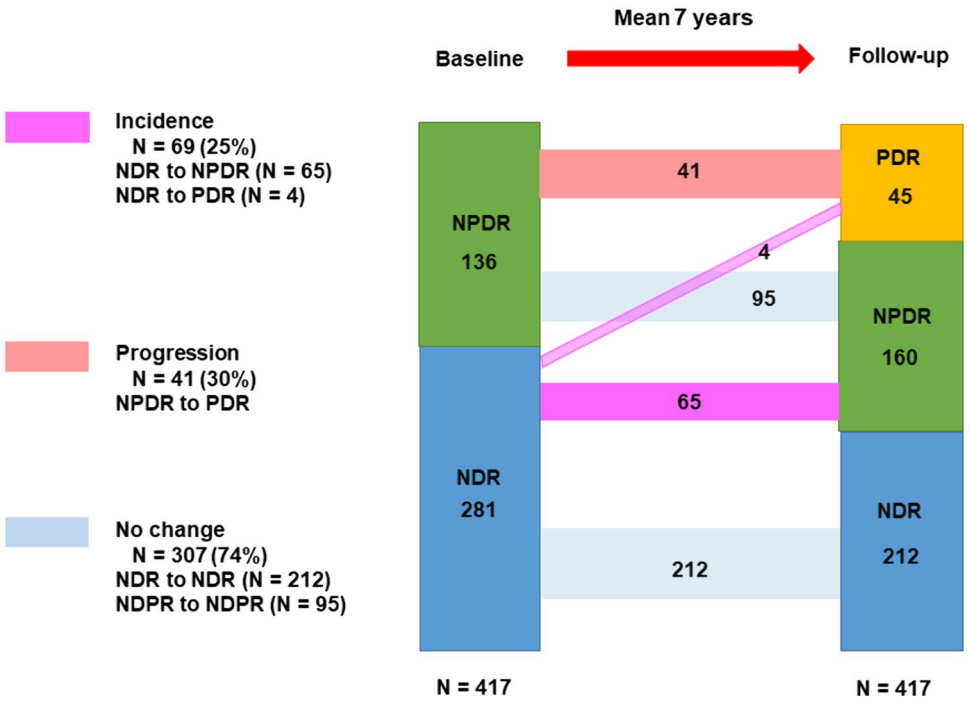

Fig. 2 Distribution of patients with T2DM on the stage of DR at baseline and during the follow-up. Numbers of incidence are shown in the purple band, those of progression are shown in light red band and those of no changes are shown in light blue band. *NDR* no diabetic retinopathy, *NPDR* nonproliferative diabetic retinopathy, and *PDR* proliferative diabetic retinopathy

Table 2 Rate of incidence of DR and its odds ratio

	No treatment cessation	Treatment cessation	*P*
Subjects *N* = 281	248	33	
Incidence cases *N* = 69	50	19	
Incidence rate (%)	20% (50/248)	58% (19/33)	
Age and sex-adjusted odds ratio	1 (reference)	5.71 (2.59–12.57)	< 0.01
Multivariate-adjusted odds ratio	1 (reference)	4.20 (1.46–12.04)	< 0.01

A logistic regression model was used to calculate the odds ratio (95% confidence interval) with the no treatment cessation group serving as the reference after adjusting for age, sex, BMI, duration of T2DM, and HbA1c level

Table 3 Rate of progression of DR and its odds ratio

	No treatment cessation	Treatment cessation	*P*
Subjects *N* = 136	116	20	
Progression cases *N* = 41	33	8	
Progression rate (%)	28% (33/116)	40% (8/20)	
Age and sex-adjusted odds ratio	1 (reference)	1.64 (0.61–4.41)	0.32
Multivariate-adjusted odds ratio	1 (reference)	1.72 (0.56–5.34)	0.35

A logistic regression model was used to calculate the odds ratio (95% confidence interval) with the no treatment cessation group serving as the reference after adjusting for age, sex,BMI, duration of T2DM, and HbA1c level

between two groups [26]. Archibald et al. reported from the UK that 37 patients (Type 1 diabetes mellitus and T2DM) with treatment cessation showed both a higher level of HbA1c and a higher prevalence of microvascular and macrovascular complications as compared to the other 37 patients with non-cessation [32]. In 1985, Hammersley et al. reported that treatment cessation was associated with the subsequent occurrence of DR in 54 patients with T2DM, and there were positive correlations between the occurrence of DR and higher levels of HbA1c or diastolic blood pressure [27]. Importantly, however, the study showed the association of interest without allowing for clinical characteristics related

Table 4 Rate of incidence and progression of DR and its odds ratio

	No treatment cessation	Treatment cessation	*P*
Subjects $N=417$	364	53	
Incidence and progression cases $N=110$	83	27	
Incidence annd progression rate (%)	23% (83/364)	51% (27/53)	
Age and sex-adjusted odds ratio	1 (reference)	3.48 (1.91–6.35)	<0.01
Multivariate-adjusted odds ratio	1 (reference)	2.70 (1.28–5.69)	<0.01

A logistic regression model was used to calculate the odds ratio (95% confidence interval) with the no treatment cessation group serving as the reference after adjusting for age, sex, BMI, duration of T2DM, and HbA1c level

to treatment cessation [27]. Unlike these previous studies, to the best of our knowledge, the present study would be the first cohort study that demonstrates an association between treatment cessation and the incidence (incidence/progression) of DR after adjusting for a variety of confounders using multivariate analyses (Tables 2, 4). In consistent with a line of previous reports [1–3], a higher level of HbA1c was also significantly associated with the incidence of DR (Supplemental Table 1). Longer duration of T2DM and higher levels of HbA1c were significantly associated with the incidence/progression of DR (Supplemental Table 3). Consequently, the association between treatment cessation and the incidence (incidence/progression) of DR was independent of these clinical characteristics. It was notable that the association of interest was independent of increased HbA1c which is somewhat linked with treatment cessation. However, our study only provides evidence on the association of interest, and precise molecular mechanisms whereby treatment cessation would induce DR still remain unsolved. In the present study, with a sharp contrast to the case of incidence of DR, treatment cessation was not significantly associated with progression of DR. It has been reported that sustained hypertension coupled with a higher level of HbA1c is apparently associated with the incidence of DR. In contrast, continuously high level of HbA1c per se has been shown to be associated with the progression of DR [4, 33]. This notion may suggest that the incidence of DR is influenced by a variety of factors in a complexed fashion, whereas the progression of DR would mainly depend on the quality of glycemic control. In this sense, prospective clinical studies are warranted to clarify the differences in risk factors between incidence and progression of DR.

As the present study was conducted using preexisting medical records and treatment cessation was retrospectively checked, it has some limitations. For example, blood examinations before and after treatment cessation could not be precisely evaluated, and all examinations in the follow-up period were undertaken at different time schedules for each patient. Thus, we could not examine whether treatment cessation results in poor metabolic control. The incidence of DR in each case may differ depending on the timing of cessation in the course of treatment. There seem to be two major scenarios on the possible association between treatment cessation and incidence of DR. First, in case treatment was ceased early in the course of treatment, transient hyperglycemia would impact the aggravation of later complications, also known as the notion of "negative legacy effects" [34–37]. It has been suggested that mechanisms of the negative legacy effects are tightly linked with epigenetic modifications and exaggerated chronic oxidative stress [38–40]. Second, in case the treatment cessation occurred later in the course of treatment and also hyperglycemia improved rapidly after resuming treatment, DR is likely to worsen expeditiously, also known as the notion of "accelerated worsening of DR" [41–43]. The mechanisms of accelerated worsening of DR have been shown, at least partly, to link with the disruption of the autoregulation of capillary blood flow at the retina [44].

In accordance with the previous reports, the prevalence of treatment cessation in the present study was 13% (Table 1). The prevalence of treatment cessation ranges from 4 to 19% in the UK [28, 32], 12–50% in the United States [45, 46], and 35–57% in Japan [47, 48]. Characteristics of the treatment cessation group in our data are relative youth as compared to the nontreatment cessation group (Table 1). Our data are in agreement with many previous reports in terms of relative youth [9–12], further confirming the validity of the cohort in the present study.

We do acknowledge that there are a couple of critical limitations in the present study. First, because of the retrospective design, the present study failed to obtain a considerable amount of clinical data, and also the duration of treatment cessation or clinical parameters before and after cessation or precise severity of DR could not be adequately considered. Various clinical factors such as the value of HbA1c during the course of follow-up may also influence the development of DR. Also, we do recognize the importance of a multivariate model including time-dependent HbA1c level. However, just because the data of the present study are anonymously obtained, we are sorry to have to say that we cannot detect new data at this time. Second, our study did not investigate the detailed

therapeutic framework and the underlying reasons for treatment cessation. Finally, we did not examine the relationship between treatment cessation and other diabetic complications including neuropathy, nephropathy, and macroangiopathy.

In summary, our data highlight that, independently of glycemic control and duration of the disease, treatment cessation increases the incidence risk of DR in patients with T2DM. Further studies are warranted to clarify the underlying mechanisms of the causal relationship between treatment cessation and the incidence of DR, which should help to prevent the incidence of DR.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13340-024-00724-7.

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Author contributions All authors contributed to the study's conception and design. Material preparations were performed by Yoshiro Nakayama, Moritake Higa, Hideki Koizumi, Michio Shimabukuro, and Hiroaki Masuzaki, data collections were performed by Yoshiro Nakayama and Moritake Higa, and analyses were performed by Yukiko Shinzato, Yoshiro Nakayama, Tsugumi Uema, Hideki Koizumi, Michio Shimabukuro, Koshi Nakamura, and Hiroaki Masuzaki. The first draft of the manuscript was written by Yukiko Shinzato, Yoshiro Nakayama, Jasmine F Millman, Michio Shimabukuro, and Hiroaki Masuzaki, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of interest None of the authors have any conflicts of interest to disclose.

Ethical approval All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (The Ethics Committee of University of the Ryukyus for Medical and Health Research Involving Human Subjects (No.765) on February 27, 2015) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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