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SHORT REPORT

Changes of HbA1c variability after the switch to a longer-acting insulin analog in people with type 1 diabetes

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ABSTRACT

This study investigated whether longer-acting basal analogs (insulin degludec and insulin glargine U300) could reduce visit-to-visit hemoglobin A1c (HbA1c) variability in patients with type 1 diabetes. Ninety adults with type 1 diabetes for whom the basal insulin was switched to a longer-acting insulin analog were analyzed retrospectively. The coefficient of variation of HbA1c levels (CV-HbA1c) during the year before and after the switch was compared. The CV-HbA1c after the switch was not significantly different from that before the switch (4.39 ± 2.24% vs 4.25 ± 2.07%; $P = 0.506$). The linear regression model revealed that CV-HbA1c before the switch was independently associated with the change of CV-HbA1c (regression coefficient per standard deviation = –0.568, $P < 0.001$), whereas the other variables were not (all $P > 0.05$). In conclusion, CV-HbA1c remained unchanged after the switch on average, but CV-HbA1c before the switch was associated with the decrease of CV-HbA1c in individuals with type 1 diabetes.

INTRODUCTION

Type 1 diabetes is characterized by insulin deficiency, causing hyperglycemia, and is associated with chronic diabetes complications[1]. Sustained high hemoglobin A1c (HbA1c) levels were classically demonstrated as a risk factor for chronic complications[2]. Recently, visit-to-visit HbA1c variability has additionally been highlighted. Clinical studies identified not only long-term glycemic control, assessed by mean HbA1c levels, but also visit-to-visit HbA1c variability, assessed by their coefficient of variation (CV) or standard deviation (SD), as an independent risk factor for chronic complications[3–5]. Thus, therapies reducing visit-to-visit HbA1c variability in type 1 diabetes are awaited.

Recently, insulin degludec and insulin glargine U300 have become clinically available. These newer basal analogs are referred to as "longer-acting basal analogs"[6], and could contribute to lowering the risk of hypoglycemia and reducing daily glycemic variability in individuals with type 1 diabetes[7–10]. Daily glycemic variability would be associated with visit-to-visit HbA1c variability[11]. However, whether these new insulin analogs, associated with lower daily glycemic variability, would also reduce visit-to-visit HbA1c variability was not known. The current study aimed to determine the change of HbA1c variability after the switch to longer-acting insulin analogs, and to identify factors associated with the change in people with type 1 diabetes.

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METHODS

Study population

Ninety adults with type 1 diabetes attending the department of Metabolic Medicine, Osaka University Hospital, in whom their basal insulin was switched to longer-acting insulin analogs between 2013 and 2019, were analyzed retrospectively. All data were extracted from the existing electronic medical records. Details of the study population are presented in the Supplemental Methods.

Mean and CV of HbA1c

The mean HbA1c levels (Mean-HbA1c) and the CV of HbA1c levels (CV-HbA1c) before the switch were calculated using the HbA1c levels measured during the year before the switch, and those after the switch were calculated using HbA1c levels measured between 3 and 15 months after the switch. Details of the calculations are presented in the Supplemental Methods.

Statistical analysis

Data on the clinical characteristics are shown as the mean ± SD for continuous variables or percentages for discrete variables. A value of $P < 0.05$ was considered statistically significant. Mean-HbA1c and CV-HbA1c before and after the switch were compared by the paired *t*-test. The association of baseline characteristics with the change of Mean-HbA1c and CV-HbA1c was investigated using simple or multiple linear regression models. The explanatory variables in the multiple models were determined as those with statistical significance in the single regression model. All statistical analysis was performed using R version 4.0.3 (R Development Core Team, Vienna, Austria).

RESULTS

The baseline characteristics of the study population are shown in Table 1. No significant differences in the patients' characteristics were observed between the two longer-acting insulin analogs (Table S1). The insulin dose was not significantly changed after the switch, whereas the number of individuals injecting basal insulin twice per day was significantly decreased (Table S2). The Mean-HbA1c and CV-HbA1c after the switch were not significantly different from those before the switch (7.72 ± 0.88% vs 7.69 ± 0.94% and 4.39 ± 2.24% vs 4.25 ± 2.07%; $P = 0.648$ and $P = 0.506$, respectively). Similar findings were observed regardless of the type of longer-acting analog (Table S3), and after limiting the population to individuals whose bolus insulin was unchanged and those in whom undetectable C peptide levels were confirmed (Table S4). Table 2 demonstrates the association of baseline characteristics with the change of Mean-HbA1c and CV-HbA1c. In the single linear regression model, the HbA1c levels at the switch, the Mean-HbA1c before the switch, and the CV-HbA1c before the switch were inversely associated with the change of the Mean-HbA1c. On the other hand, the HbA1c levels at the switch and the CV-HbA1c before the switch were inversely associated with the change of CV-HbA1c. In the multivariate model, CV-HbA1c before the switch was independently associated with the change of Mean-HbA1c and CV-HbA1c (regression coefficient [*B*] per 1 SD = −0.370 and −0.568, both $P < 0.001$). Similar findings were observed when either HbA1c levels at the switch or the Mean-HbA1c before the switch was excluded from the multivariate model to avoid the risk of their multicollinearity (data not shown). The SD of HbA1c (SD-HbA1c) was also unchanged after the switch (0.33 ± 0.16% vs 0.34 ± 0.20%, $P = 0.413$), and SD-HbA1c before the switch was independently associated with the change of SD-HbA1c (*B* per 1 SD = −0.762, $P < 0.001$) (Table S5).

Table 1 | Clinical characteristics of study population at the switch to a longer-acting insulin analog (baseline) ($n = 90$)

Age, (years)	54 ± 13
Men, *n* (%)	43 (47.8)
Duration of diabetes, (years)	21 ± 12
Body mass index, (kg/m^2)	22.4 ± 3.1 (data missing, $n = 1$)
eGFR (mL/min/1.73m^2)	80.3 ± 16.8 (data missing, $n = 1$)
HbA1c levels at the switch, (%)	7.79 ± 1.06
Season at the switch, *n* (%)	
Spring (from March to May)	21 (23.3)
Summer (from June to August)	14 (15.6)
Autumn (from September to November)	29 (32.2)
Winter (from December to February)	26 (28.9)
Total bolus insulin dose, (units/day)	28 ± 12
Total basal insulin dose, (units/day)	13 ± 8
Number of basal insulin injections	
Twice per day, *n* (%)	34 (37.8)
Once per day at breakfast, *n* (%)	10 (11.1)
at dinner, *n* (%)	16 (17.8)
at bedtime, *n* (%)	30 (33.3)
Basal insulin before switching	
Insulin glargine U100, *n* (%)	68 (75.6)
Insulin detemir, *n* (%)	18 (20.0)
NPH insulin, *n* (%)	4 (4.4)
Bolus insulin before switching	
Insulin aspart, *n* (%)	46 (51.1)
Insulin lispro, *n* (%)	27 (30.0)
Insulin glulisine, *n* (%)	4 (4.4)
Regular insulin, *n* (%)	13 (14.4)
Type of diabetes	Data missing, $n = 38$
Fulminant, *n* (%)	6 (6.7)
Acute onset, *n* (%)	39 (43.3)
SPIDDM, *n* (%)	7 (7.8)
Individuals in whom undetectable C peptide levels were confirmed, *n* (%)	56 (62.2)

Data are shown as mean ± standard deviation or frequency (percentage). eGFR, estimated glomerular filtration rate; NPH, neutral protamine Hagedorn; SPIDDM, slow promoting insulin dependent diabetes mellitus; U100, 100 units/mL.

DISCUSSION

The current study revealed that the Mean-HbA1c and CV-HbA1c remained unchanged after the switch to longer-acting insulin analogs in people with type 1 diabetes. The current study further revealed that the change of Mean-HbA1c and CV-HbA1c were inversely associated with the CV-HbA1c before the switch. To the best of our knowledge, this is the first report on visit-to-visit HbA1c variability after the switch to longer-acting insulins.

Unchanged Mean-HbA1c after the switch would be consistent with previous non-inferiority trials on longer-acting insulins vs conventional basal insulin[7–10]. The current study also revealed that CV-HbA1c was unchanged after the switch. These findings were in contrast to studies on continuous subcutaneous insulin infusion (CSII) therapy, which clearly reduced the mean and CV of HbA1c levels in adults with type 1 diabetes[12]. Longer-acting insulins *per se* may not have such beneficial effects on the reduction of Mean-HbA1c and CV-HbA1c

Table 2 | Association of baseline characteristics with the change of mean and CV of HbA1c

	Mean of HbA1c				CV of HbA1c			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	B	*P*	*B*	*P*	*B*	*P*	*B*	*P*
Age	0.083	0.437	–	–	−0.077	0.468	–	–
Men (vs Women)	0.094	0.346	–	–	−0.224	0.603	–	–
Duration of diabetes	−0.115	0.281	–	–	−0.106	0.320	–	–
Body mass index	0.162	0.133	–	–	0.103	0.335	–	–
eGFR	−0.000	0.996	–	–	0.088	0.412	–	–
HbA1c levels at the switch	−0.303	0.005	0.113	0.289	−0.242	0.025	−0.087	0.413
Mean of HbA1c during the previous year	−0.403	<0.001	−0.231	0.032	−0.210	0.051	–	–
CV of HbA1c during the previous year	−0.477	<0.001	−0.370	<0.001	−0.627	<0.001	−0.568	<0.001
Season at the switch		0.531				0.575		
Spring (vs mean)	0.087		–	–	0.335		–	–
Summer (vs mean)	−0.096		–	–	−0.224		–	–
Autumn (vs mean)	0.066		–	–	0.252		–	–
Winter (vs mean)	−0.057		–	–	−0.039		–	–
Total bolus insulin dose	−0.033	0.758	–	–	−0.088	0.406	–	–
Total basal insulin dose	−0.079	0.460	–	–	0.150	0.161	–	–
Number of basal insulin injections	0.005	0.963	–	–	0.039	0.711	–	–
Basal insulin before switching		0.362				0.341		
Insulin glargine U100 (vs mean)	0.066		–	–	0.525		–	–
Insulin detemir (vs mean)	−0.1112		–	–	0.486		–	–
NPH insulin (vs mean)	0.046		–	–	−1.011		–	–

The associations were determined using single linear regression models (unadjusted models), and multiple linear regression models (adjusted models). Cases with missing data were addressed by the listwise deletion in respective models. In the multivariate model, HbA1c levels before switching, mean of HbA1c during the previous year, and CV of HbA1c during the previous year were entered as the explanatory variables in the change of mean of HbA1c, and HbA1c levels before switching and CV of HbA1c during the previous year were entered as the explanatory variables in the change of CV of HbA1c. *B*, regression coefficient determined by single or multiple linear regression models. For continuous variables, regression coefficients per 1 SD were shown. For the binary variable (sex), the regression coefficient corresponded to the difference of men from women. For other discrete variables (seasons and basal insulin before switch), regression coefficients were obtained using the deviation contrast coding, indicating the difference from the overall mean. The values of *P* were calculated using analysis of variance (ANOVA); CV, coefficient of variation; eGFR, estimated glomerular filtration rate; NPH; neutral protamine Hagedorn; U100, 100 units/mL.

in the overall population as CSII. On the other hand, the current study also revealed that the change of Mean-HbA1c and CV-HbA1c was inversely associated with CV-HbA1c before the switch. The current findings indicated that the switch to longer-acting insulins might be effective for individuals in people with type 1 diabetes whose CV-HbA1c were high, while HbA1c control might deteriorate in people already achieving sufficiently low Mean-HbA1c and CV-HbA1c by conventional basal insulins. Utilizing the information of the past CV-HbA1c might be helpful in selecting individuals in whom the switch to a longer-acting insulin would be advantageous, and thus in improving HbA1c control in the whole population with type 1 diabetes.

Our study has several limitations. First, this was a single-center study, and the sample size was limited. Second, the current study was an observational one and could not prove causal relationships. Third, limited data were available on the participants' attributes, including insulin resistance, residual beta-cell function, episodes of hypoglycemia, and the subtype of type 1 diabetes. Fourth, our study design was not to reveal a difference between two longer-acting insulins. Furthermore, the current study lacked matched controls whose basal insulin was not switched to longer-acting insulins. Future studies will be needed to validate the current findings.

In conclusion, Mean-HbA1c and CV-HbA1c remained unchanged after the switch to longer-acting insulin analogs in individuals with type 1 diabetes. The change of Mean-HbA1c and CV-HbA1c were inversely associated with CV-HbA1c before the switch.

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DISCLOSURE

H. Watanabe declares no conflict of interest. M. Takahara has received lecture fees from Sanofi K.K. N. Katakami has received

lecture fees from Sanofi K.K and Novo Nordisk Pharma. I. Shimomura has received consulting fees and/or speakers' bureau and scholarship grants from Sanofi K.K and Novo Nordisk Pharma.

Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted Ethics Committee of the institution and it conforms to the provisions of the Declaration of Helsinki. Committee of the Institutional Review Board of Osaka University Hospital, Approval No. 16136–4.

Informed consent: On the grounds that the current study was an observational research study using only existing materials, the study was considered exempt from informed consent of people, in accordance with the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1 | Details of the study population.

Appendix S2 | Details of the calculation of mean and CV of HbA1c.

Table S1 | Characteristics of study population at the switch to a longer-acting insulin analog (n = 90).

Table S2 | Change of insulin component after the switch to a longer-acting insulin analog.

Table S3 | The difference in the change of mean and CV of HbA1c between insulin degludec and insulin glargine U300.

Table S4 | Subgroup analysis of the difference in the change of mean and CV of HbA1c in participants whose bolus insulin was unchanged (n = 86), and those in whom undetectable C peptide levels were confirmed (n = 56).

Table S5 | Association of baseline characteristics with the change of SD of HbA1c.