Association Between the Variability of Glycated Hemoglobin and Retinopathy in Patients with Type 2 Diabetes Mellitus: A Meta-Analysis

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ABSTRACT

Visit-to-visit variability of glycated hemoglobin (HbA1c) is a marker of long-term glycemic fluctuation, which has been related to increased risk of macrovascular complications in patients with type 2 diabetes mellitus (T2DM). The association between HbA1c variability and retinopathy in patients with T2DM, however, has been inconsistent in previous studies. In order to fully evaluate the above association, we conducted a meta-analysis. Observational studies related to the aim of the meta-analysis were identified by search of PubMed, Web of Science, and Embase databases. Studies with HbA1c variability evaluated as the standard deviation (SD) and/or the coefficients of variation (CV) of HbA1c were included. The results were analyzed using a random-effects model that incorporated potential heterogeneity between studies. Twelve observational studies involving 44 662 T2DM patients contributed to the meta-analysis. Overall, 5150 (11.5 %) patients developed retinopathy. Pooled results showed that compared to patients with lower HbA1c variability, T2DM patients with higher HbA1c-SD (relative risk [RR]: 1.48, 95 % confidence interval [CI]: 1.24 to 1.78, $p < 0.001$, $I2 = 34$ %) and higher HbA1c-CV (RR: 1.29, 95 % CI: 1.05 to 1.59, $p = 0.02$, $I2 = 0$ %) were both associated with higher risk of DR. For studies with HbA1c-SD, the association was not significantly affected by study characteristics such as country, study design, mean age, disease duration, adjustment of mean HbA1c, or quality scores (p for subgroup difference all > 0.05). In conclusion, higher HbA1c variability may be associated with an increased risk of retinopathy in patients with T2DM.

Introduction

Patients with type 2 diabetes mellitus (T2DM) are at risk for diabetic retinopathy (DR), a serious condition that can cause severe vision problems [1–3]. Moreover, DR has been linked to an increased risk for various adverse outcomes in T2DM patients, such as non-fatal myocardial infarction, stroke, and cardiovascular mortality [4, 5]. Although persistent hyperglycemia has been well recognized as a major cause of vascular complications in patients with T2DM, accumulating evidence suggests that in addition to average blood glucose levels, glycemic variability, which is defined as how glycemic levels fluctuate over time, may also be associated with vascular complications [6–8]. Clinically, glycemic variability could be measured in short-term (over days or weeks) or long-term manners depending on duration of observation [9–11]. However, glycemic variability does not yet have a standard definition or measurement method [9–11]. For determining long-term glycemic

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variability, most previous studies used the standard deviation (SD) or coefficient of variation (CV) of glycated hemoglobin (HbA1c) [12]. Interestingly, a recent meta-analysis of twelve longitudinal follow-up studies showed that long-term glycemic variability as evidenced by the increased HbA1c-SD or HbA1c-CV may be an independent risk factor for cardiovascular events in patients with T2DM [13]. Moreover, it has been also suggested that diabetic patients with higher HbA1c variability are more likely to develop dementia [14]. Despite this, previous studies examining the association between HbA1c variability and the risk of DR showed inconsistent results [15–26]. In some studies, higher HbA1c variability appeared to be independently associated with DR [21, 24, 26], while in other studies, the association was not significant [15–20, 22, 23, 25]. The purpose of this study was therefore to investigate whether visit-to-visit HbA1c variability is associated with DR among patients with T2DM by performing a meta-analysis.

Materials and Methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [27, 28] and the Cochrane's Handbook [28] guidelines.

Database search

Studies were retrieved by search of the electronic databases including PubMed, Web of Science, and Embase databases from inception to May 4, 2022, with a combined search terms of (1) "glycemic" OR "glyceamic" OR "glucose" OR "hemoglobin A1c" OR "A1C"; (2) "variability" OR "variation" OR "fluctuation"; and (3) "retina" OR "retinal" OR "retinopathy". There was no restriction on the publication language, only human studies were searched. A manual screening of references from relevant original and review articles was also conducted. During the meta-analysis, only full-length articles published in peer-reviewed journals were included.

Study inclusion and exclusion criteria

A PICOS-recommended set of inclusion criteria was developed based on the meta-analysis's purpose.

P (participants): Adult patients (18 years old or above) with T2DM.

I (exposure): Patients with higher visit-to-visit HbA1c variability, as evaluated by higher standard deviation (SD) and/or the coefficients of variation (CV) of HbA1c.

C (control): Patients without lower visit-to-visit HbA1c variability, as evaluated by lower HbA1c-SD and/or HbA1c-CV.

O (outcomes): Relative risk of DR compared between T2DM patients with the highest versus the lowest category of HbA1c variability. The cutoffs for the defining the highest versus the lowest category of HbA1c variability were consistent with the values used in the original articles.

S (study design): Observational studies, which include case-control studies, cross-sectional studies, and cohort studies.

Reviews, meta-analyses, editorials, preclinical studies, studies including children, studies including non-T2DM patients, studies that did not evaluate HbA1c variability, or studies that did not report the outcome of DR were excluded. We did not include grey literatures because most of these literatures (conference abstracts, unpublished data etc.,) are not peer-reviewed, and including these studies may affect the validity of the meta-analysis results. When there was overlap in the population of two or more studies, we included the study with the largest sample size.

Data collection and quality assessing

During the research process, two authors independently analyzed literature, collected data, and assessed the quality of the study. Discrepancies were discussed with the corresponding author if they occurred. We extracted data regarding basic study information, participant characteristics, age, sex, duration of T2DM, methods for the measuring HbA1c variability, cutoffs for defining the higher and lower HbA1c variability, methods for the confirmation of DR, number of patients with DR, and variables adjusted when the association between HbA1c variability and DR was presented. As a measure of study quality, Newcastle-Ottawa scales (NOS) were used [29], on the basis of participant selection criteria, group comparison, and outcome validity. A study's quality is assessed on a scale of 1–9 stars, with a higher number of stars indicating a higher standard of study.

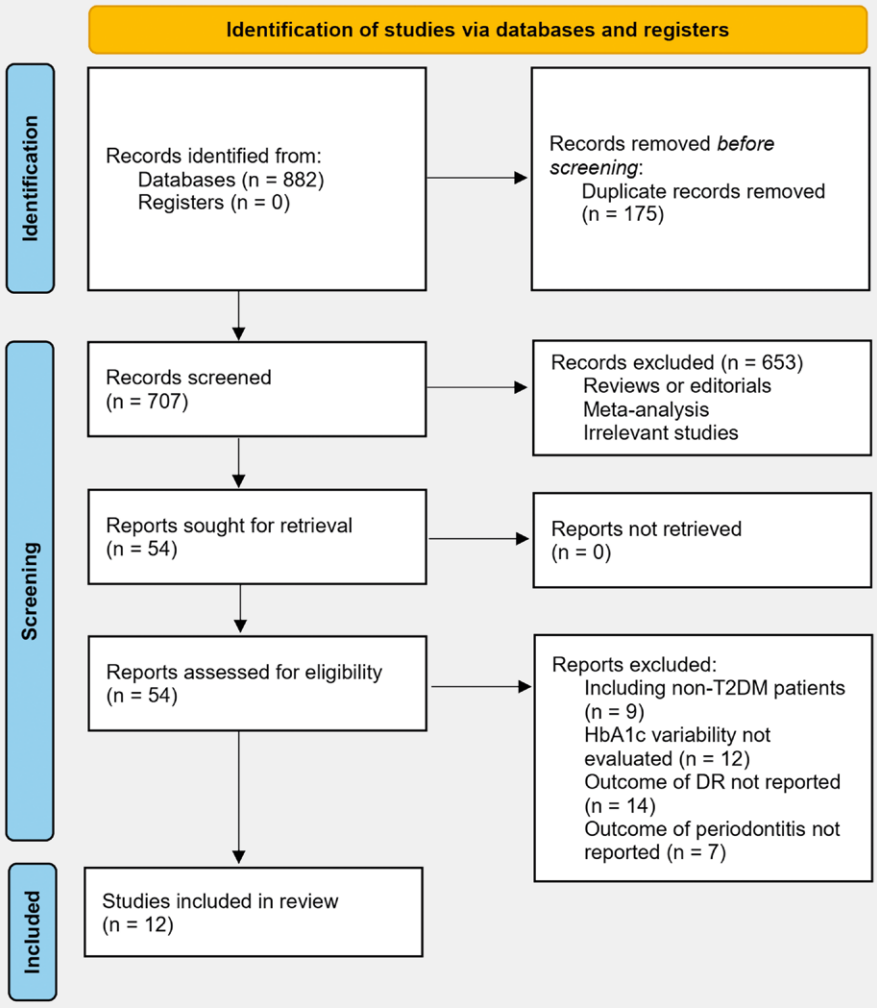
Statistics

The association between HbA1c variability (HbA1c-SD and HbA1c-CV) and the risk of DR in T2DM patients was presented as risk ratio (RR) and the 95 % confidence interval (CI). A meta-analysis was performed on the RR data derived with the most appropriately adjusted model in studies analyzing the above association. By using the 95 % confidence intervals or p-values, RRs and standard errors (SEs) could be calculated. We then transformed the distribution using logarithms in order to maintain stabilized variances and normalized distributions. Heterogeneity between studies was determined using Cochrane's Q-test and I^2 statistics [30]. The between-study heterogeneity was classed as mild ($I^2 < 25$ %), moderate (I^2 25–75 %), and high ($I^2 > 75$ %) according to the Cochrane's Handbook [28]. The results were combined using a random-effects model incorporating heterogeneity's influence [28]. Meta-analysis results were evaluated by excluding one dataset at a time to determine how individual studies influenced the results [31]. Sensitivity analysis by excluding one study at a time was performed to evaluate the influence of single study on the results of the overall meta-analysis. If at least ten studies were included, subgroup analyses could be performed to evaluate the possible influences of study characteristics on the association. An estimation of publication bias was performed using funnel plots constructed by visual judgement of symmetry, with an Egger's regression asymmetry test in addition [32]. The RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and Stata software (version 12.0; Stata Corporation, College Station, TX) were used for the statistical analyses.

Results

Literature search

The literature search and inclusion process are summarized in ▶ **Fig. 1**. Overall, 882 records were obtained from the initial database search, with 175 being removed due to duplication. After screening titles and abstracts of 707 studies, 653 were excluded largely



▶ **Fig. 1** Diagram of database search and study inclusion.

due to non-relevance to the meta-analysis's objective. Ultimately, 54 studies were reviewed in full-text, and 42 were excluded for the reasons listed in ▶ **Fig. 1**, leading to 12 studies available for the meta-analysis [15–26].

Study characteristics

▶ **Table 1** shows characteristics of the studies included. Overall, 12 observational studies, including one cross-sectional study [15], one case-control study [16], three prospective [17, 19, 23], and seven retrospective cohort studies [18, 20–22, 24–26], with 44 662 patients with T2DM, contributed to the meta-analysis. These studies were published between 2013 and 2021, and performed in Italy [15, 18], the Netherlands [19], Brazil [17], Australia [22], Scotland [21], Singapore [16], Korea [20, 25, 26], and China [23, 24], respectively. The mean ages of the patients varied between 58 and 68 years, and the duration of T2DM ranged from < 1 year to 15 years. Variability of HbA1c was analyzed using HbA1c-SD in ten studies [15–18, 20–24, 26], and using HbA1c-CV in six studies [17, 19, 21–23, 25]. At least 3 HbA1c measurements within 2 ~ 5 years were used for the determination of HbA1c variability in the included studies. The cutoffs for categorizing HbA1c variability varied among the included studies, with medians [16, 18, 20, 24], tertiles [17, 23], quartiles [15, 22, 25, 26], or quintiles [19, 21]. The follow-up durations for the cohort studies varied from 3 to 15 years. The confirmation of DR was performed by ophthalmologist with fundus or retinal photographs. Overall, 5150 (11.5 %) patients developed retinopathy. Possible confounding factors such as age, sex, body mass index (BMI), duration of DM, comorbidities, antidiabetic treatments, and mean HbA1c were adjusted to a varying degree among the included studies. Studies included in this review received a total of seven to nine stars according to the NOS, suggesting a generally high level of study quality (▶ **Table 2**).

Meta-analysis results

A meta-analysis with ten studies [15–18, 20–24, 26] showed that T2DM patients with higher HbA1c-SD were associated with higher risk of DR (RR: 1.48, 95 % CI: 1.24 to 1.78, $p < 0.001$; ▶ **Fig. 2a**) with moderate heterogeneity (p for Cochrane's Q-test = 0.14, $I^2 = 34\,\%$). Sensitivity analysis by excluding one study at a time showed consistent results (RR: 1.38–1.54, p all < 0.05). Subgroup analysis

▶ **Table 1** Characteristics of the included studies.

Study [Ref]	Country	Study design	Sample size	Mean age (years)	Male (%)	T2DM duration (years)	Measurements for HbA1c variability	Cutoffs for HbA1c variability	Times and durations of HbA1c measurements	Follow-up duration (years)	Confirmation of DR	No. of patients with DR	Variables adjusted
Penno 2013 [15]	Italy	CS	8260	68	57	14	HbA1c-SD	Q4:Q1	3–5 times within 2 years	NA	Fundus photograph	1991	Age, BMI, sex, disease duration, smoking, TG, HDL-c, HTN, dyslipidemia, previous MACEs, treatments, and eGFR and albuminuria categories
Foo 2017 [16]	Singapore	CC	398	61	77	8	HbA1c-SD	Median	3–6 times within 2 years	NA	Fundus photograph	172	Age, sex, ethnicity, disease duration, SBP, and mean HbA1c
Cardoso 2018 [17]	Brazil	PC	654	60	38	8	HbA1c-SD and HbA1c-CV	T3:T1	At least 3 times within 2 years	9.3	Fundus photograph	152	Age, sex, number of HbA1c measurements, disease duration, BMI, smoking, physical inactivity, HTN, treatments, HDL- and LDL cholesterol, and mean HbA1c
Teliti 2018 [18]	Italy	RC	900	67	57	10	HbA1c-SD	Median	At least 3 times within 2 years	3	Fundus photograph	108	Age, sex, disease duration, BMI, TC, HDL-c, TG, smoking, HTN, dyslipidemia, treatments, and occurrence of MACEs
Slieker 2019 [19]	The Netherlands	PC	3963	62	53	1	HbA1c-CV	Q5:Q1	5 times within 5 years	15	Fundus photograph	182	Age, sex, BMI, mean HDL-c, TG, mean HbA1c, hypoglycemic treatments and eGFR
Song 2019 [20]	Korea	RC	604	61	54	14	HbA1c-SD	Median	Every 3–6 months once for 3 years	3	Fundus photograph	67	Age, sex, BMI, disease duration, smoking, comorbidities, TG, HDL-c LDL-c, insulin use, eGFR, and mean HbA1c
Li 2020 [21]	Scotland	RC	15067	63	55	Within 1 year	HbA1c-SD and HbA1c-CV	Q5:Q1	At least 5 times within 3 years	6.8	Retinal photograph	414	Age, sex, BMI, smoking, HTN, HDL-c, eGFR, CCI, and antiplatelet treatment

▶ **Table 1** Continued

Study [Ref]	Country	Study design	Sample size	Mean age (years)	Male (%)	T2DM duration (years)	Measurements for HbA1c variability	Cutoffs for HbA1c variability	Times and durations of HbA1c measurements	Follow-up duration (years)	Confirmation of DR	No. of patients with DR	Variables adjusted
Scott 2020 [22]	Australia	RC	9790	62	63	4	HbA1c-SD and HbA1c-CV	Q4:Q1	At least 3 times within 2 years	5	Retinal photograph	814	Age, sex, mean HbA1c, fenofibrate or placebo allocation, SBP, diabetes duration, prior CVD, prior microvascular complications, and antidiabetic treatments
Dai 2021 [23]	China	PC	315	58	61	11	HbA1c-SD and HbA1c-CV	T3:T1	At least 3 times within 2 years	3.4	Fundus photograph	81	Age, sex, BMI, WC, disease duration, SBP, TG, LDL-c, HDL-c, eGFR, UACR, smoking, antidiabetic treatments, and mean HbA1c
Hu 2021 [24]	China	RC	3152	67	48	15	HbA1c-SD	Median	At least 5 times within 2 years	4	Fundus photograph	556	Age, sex, BMI, disease duration, SBP, DBP, family history, smoking, alcohol drinking, antidiabetic treatments, and mean HbA1c
Park 2021 [26]	Korea	RC	1125	68	52	14	HbA1c-SD	Q4:Q1	At least 3 times within 5 years	8.5	Fundus photograph	535	Age and sex
Kim 2021 [25]	Korea	RC	434	57	55	7	HbA1c-CV	Q4:Q1	At least 3 times within 2 years	7.5	Fundus photograph	78	Age, sex, disease duration, BMI, HTN, HGB, mean HbA1c, SCr, HDL-c, LDL-c, TG, and antidiabetic treatments

T2DM: Type 2 diabetes mellitus; HbA1c: Glycated hemoglobin; DR: Diabetic retinopathy; CS: Cross-sectional; CC: Case-control; PC: Prospective cohort; RC: Retrospective cohort; SD: standard deviation; CV: Coefficients of variation; Q4:Q1: The fourth versus the first quartiles; Q5:Q1: The fifth versus the first quintiles; T3:T1: The third versus the first tertiles; NA: Not applicable; BMI: Body mass index; HTN: Hypertension; TC: Total cholesterol; TG: Triglyceride; LDL-c: Low-density lipoprotein cholesterol; HDL-c: High-density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; MACEs: Major adverse cardiovascular events; eGFR: Estimated glomerular filtrating rate; CCI: Carlson Comorbidity Index; CVD: Cardiovascular disease; WC: Waist circumference; UACR: Urinary albumin to creatinine ratio; SCr: Serum creatinine; HGB: Hemoglobin;

▶ **Table 2** Details of study quality evaluation via the Newcastle-Ottawa Scale.

Cross-sectional or case-control study	Adequate definition of cases	Representativeness of the cases	Selection of controls	Definition of controls	Control for age and sex	Control for other confounding factors	Assessment of exposure	Same methods for outcome assessment	Non-response rate	Total
Penno 2013	1	1	1	1	1	1	1	1	1	9
Foo 2017	1	0	1	1	1	1	1	1	1	8
Cohort study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at baseline	Control for age and sex	Control for other confounding factors	Assessment of outcome	Enough long follow-up duration	Adequacy of follow-up of cohorts	Total
Cardoso 2018	1	1	1	1	1	1	1	1	1	9
Teliti 2018	0	1	1	1	1	1	1	0	1	7
Slieker 2019	1	1	1	1	1	1	1	1	1	9
Song 2019	0	1	1	1	1	1	1	0	1	7
Li 2020	0	1	1	1	1	1	1	1	1	8
Scott 2020	0	1	1	1	1	1	1	1	1	8
Dai 2021	1	1	1	1	1	1	1	0	1	8
Hu 2021	0	1	1	1	1	1	1	0	1	7
Park 2021	0	1	1	1	1	0	1	1	1	7
Kim 2021	0	1	1	1	1	1	1	1	1	8

showed that the association was not significantly affected by study characteristics such as country, study design, mean age, disease duration, cutoffs for defining the categories of HbA1c-SD, adjustment of mean HbA1c, or quality scores (p for subgroup difference all > 0.05, ▶ **Table 3**). However, a stronger association between higher HbA1c-SD and DR was suggested in studies with HbA1c-SD derived from HbA1c data within 3–5 years as compared to those from HbA1c data within 2 years (RR: 2.48 vs. 1.35, p for subgroup difference = 0.04, ▶ **Table 3**). Further meta-analysis with six studies [17, 19, 21–23, 25] also showed that T2DM patients with higher HbA1c-CV had higher risk of DR (RR: 1.29, 95 % CI: 1.05 to 1.59, p = 0.02; ▶ **Fig. 2b**) with mild heterogeneity (p for Cochrane's Q-test = 0.97, I^2 = 0 %). Sensitivity analysis by excluding one study at a time did not significantly change the results (RR: 1.26–1.33, p all < 0.05).

Publication bias

The funnel plots for the meta-analyses of HbA1c evaluated with HbA1c-SD and HbA1c-CV are shown in ▶ **Fig. 3a, b**. According to visual inspection, the plots were symmetrical, reflecting low publication bias risk. The Egger's regression testing confirmed these findings (p = 0.29 and 0.47, respectively).

Discussion

In this meta-analysis of 12 observational studies, we found that T2DM patients with higher HbA1c variability is associated with increased risk for DR, and the results were consistent for studies with HbA1c variability evaluated by HbA1c-SD and HbA1c-CV. Further sensitivity analyses by excluding one study at a time showed consistent results, suggesting that the finding of the meta-analysis is stable. For meta-analysis of studies with HbA1c-SD, results showed that the association between higher HbA1c-sd and DR was not significantly affected by study characteristics such as country, study design, mean age, disease duration, adjustment of mean HbA1c, or quality scores. However, a stronger association was shown in studies with HbA1c-SD derived from HbA1c data within 3–5 years as compared to those from HbA1c data within 2 years. Collectively, these results suggest that higher HbA1c variability may be associated with an increased risk of DR in patients with T2DM.

To the best of our knowledge, few meta-analyses have been performed to determine the possible relationship between HbA1c variability and DR in patients with T2DM. An early meta-analysis in 2015 with three studies of type 1 diabetes mellitus (T1DM) patients failed to show that a higher HbA1c-CV was associated with DR. However, evaluating the association between HbA1c variability and DR in T2DM patients with a meta-analysis was not feasible in 2015 because only one study was available [33]. In current meta-analysis, we comprehensively searcher for the up-to-date relevant observational studies, and for the first time showed a significant association between higher HbA1c variability and increased risk of DR in T2DM patients in a meta-analysis. In addition to extensive literature search, the strengths of meta-analysis also include independent analyses with two parameters of HbA1c variability (HbA1c-

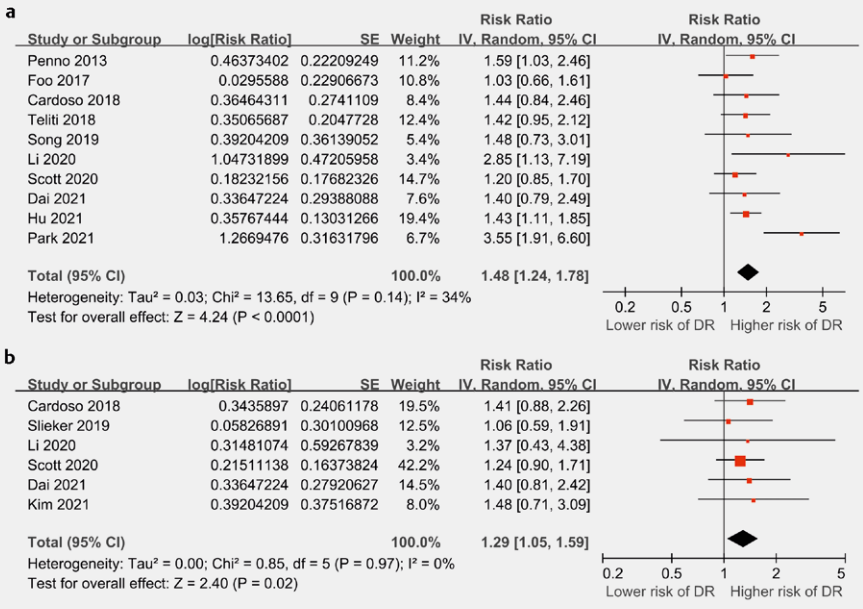
▶ **Table 3** Results of subgroup analyses for the association between HbA1c-SD and DR in patients with T2DM.

Study characteristics	Study number	RR (95% CI)	I^2	p for subgroup effect	p for subgroup difference
Country					
Asian	5	1.55 [1.09, 2.19]	61%	0.01	
Western	5	1.42 [1.16, 1.74]	0%	0.006	0.68
Study design					
PC	2	1.42 [0.96, 2.11]	0%	0.08	
RC	6	1.63 [1.23, 2.16]	55%	<0.001	
CS or CC	2	1.28 [0.84, 1.97]	46%	0.25	0.64
Mean age					
<65 years	6	1.30 [1.05, 1.60]	0%	0.01	
≥65 years	4	1.70 [1.24, 2.34]	60%	0.001	0.16
Disease duration					
<10 years	4	1.29 [0.97, 1.73]	26%	0.01	
≥10 years	6	1.60 [1.28, 2.02]	34%	<0.001	0.25
Duration for HbA1c-SD measuring					
2 years	7	1.35 [1.17, 1.57]	0%	<0.001	
3–5 years	3	2.48 [1.42, 4.32]	41%	0.001	0.04
Cutoffs for HbA1c-SD categories					
Median	4	1.35 [1.12, 1.63]	0%	0.002	
T3:T1	2	1.42 [0.96, 2.11]	0%	0.08	
Q4:Q1	3	1.80 [1.03, 3.14]	78%	0.04	
Q5:Q1	1	2.85 [1.13, 7.19]	NA	0.03	0.37
Adjustment of mean HbA1c					
Yes	6	1.32 [1.12, 1.55]	0%	0.001	
No	4	2.01 [1.31, 3.07]	58%	0.001	0.07
NOS					
7	4	1.71 [1.19, 2.44]	60%	0.003	
8–9	6	1.34 [1.10, 1.63]	0%	0.004	0.24

RR: Risk ratio; CI: Confidence interval; HbA1c-SD: Standard deviation of glycated hemoglobin; DR: Diabetic retinopathy; T2DM: Type 2 diabetes mellitus; PC: Prospective cohort; RC: Retrospective cohort; CS: Cross-sectional; CC: Case-control; NOS: Newcastle-Ottawa Scale; Q4:Q1: The fourth versus the first quartiles; Q5:Q1: The fifth versus the first quintiles; T3:T1: The third versus the first tertiles; NA: Not applicable.

SD and HbA1c-CV) and conducting of multiple sensitivity and subgroup analyses to confirm the robustness of the findings. Results of the meta-analysis support that higher HbA1c variability may be an independent risk factor of DR in patients with T2DM. Considering the severe adverse outcomes related to DR, these findings suggest that evaluation of long-term glycemic variability should be incorporated into the risk prediction for DR in patients with T2DM. Besides, results of the meta-analysis also highlighted the hypothesis whether attenuation of glucose fluctuations in patients with T2DM may reduce the risk of DR. Clinical studies should be considered in the future for further investigation.

Results of the subgroup analyses showed a stronger association in studies with HbA1c-SD derived from HbA1c data within 3–5 years as compared to those from HbA1c data within 2 years. This may reflect the fact that glycemic fluctuation during a longer period may lead to severer pathophysiological changes on retina in these patients. Besides, the association between HbA1c-SD and DR seemed to be reduced but still significant in studies with adjustment of mean HbA1c, as compared to the association in studies without adjustment of mean HbA1c (RR: 2.01 versus 1.32, p = 0.07). These findings may suggest that both persistent hyperglycemia and long-term synergistically play key roles in the pathogenesis of DR, reflecting the importance of reducing glucose variability despite controlling of mean glucose level regarding the prevention of DR in T2DM patients. The mechanisms underlying the association between HbA1c variability and DR in patients with T2DM remain to be clarified. Previous studies have shown that increased glucose fluctuations are related to systemic inflammation [34], oxidative stress [35], and endothelial dysfunction [36], which have been all recognized as key pathogenic factors for DR [37, 38]. Additionally, a previous study in human retinal endothelial cells showed that intermittent high glucose increases cell proliferation and vascular endothelial growth factor overexpression via the overproduction of reactive oxygen species (ROS), suggesting that increased glycemic

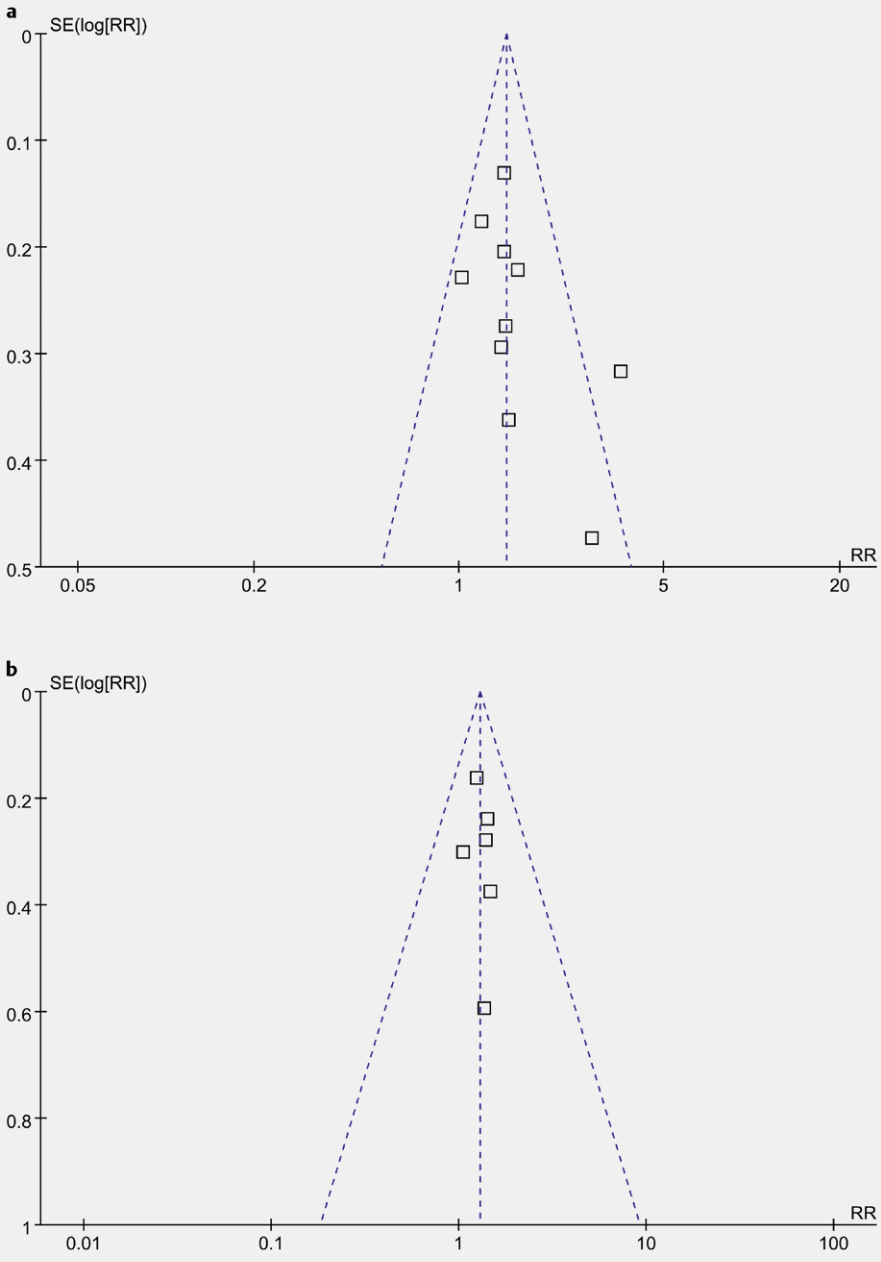


▶ **Fig. 2** Forest plots for the meta-analysis regarding the association between HbA1c variability and DR in T2DM patients. **a**: meta-analysis of HbA1c variability analyzed with HbA1c-SD and **b**: meta-analysis of HbA1c variability analyzed with HbA1c-CV.

variability may influence the pathogenesis of DR mediated by mitochondrial ROS [39]. Besides, a recent study showed that increased glucose variability may lead to dysfunction of retinal Müller cells, an early pathogenic feature of DR [40]. Studies are warranted to determine the key molecular mechanisms underlying the association between high HbA1c variability and DR in patients with T2DM.

In this study, we used HbA1c-SD and HbA1c-CV as the indicators for visit-to-visit variability of HbA1c because these two parameters are the predominantly used parameters in previous studies [12]. Besides these two parameters, a few other indicators for HbA1c variability have also been used in some of the previous studies for the predicting the risk of DR. For example, a higher HbA1c variability score (HVS), which is calculated as the percentage of the number of changes in HbA1c > 0.5 % (5.5 mmol/mol) among all HbA1c measurements within an individual, has been associated with increased risks of microvascular complications of T2DM [21]. Besides, another previous study using variability independent of the mean (VIM) and the average real variability (ARV) of HbA1c did not show a significant association between the visit-to-visit HbA1c variability and the risk of DR [23]. More studies are needed to determine if the association between long-term HbA1c variability and DR is consistent among studies using different parameters. In addition, the variability of HbA1c, in some studies, variability of fasting plasma glucose (FPG) has been applied as indicators of long-term glucose variability, which also showed a potential association with DR. An early meta-analysis with eight studies showed that high FPG variability levels were positively associated with the risk of retinopathy and all-cause mortality in patients with T2DM [41]. Consistently, a recent post-hoc analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and the Veteran Affairs Diabetes Trial (VADT) showed that variability of FPG may be an independent and readily available marker of microvascular complications in patients with T2DM [42]. Moreover, some emerging studies have also suggested a potential association between acute glucose variability measured using continuous glucose monitoring (CGM) and the microvascular complications in patients with diabetes. For example, an early study showed that acute glucose fluctuations as represented by CONGA 2 and SD in CGM was associated with DR in patients with diabetes regardless of HbA1c [43]. In addition, in a large study of patients with T2DM, the time in range (TIR) assessed by CGM is also associated with DR [44, 45]. Studies are also warranted to determine the optimal parameters for glucose variability in the future.

Some limitations exist in our meta-analysis. First, the protocols and methods for the measuring of HbA1c variability were not consistent among the included studies. Studies are needed in the future to determine the standard methods for the measurement of long-term glycemic variability and the optimized cutoffs for the defining of patients with high HbA1c variability. Besides, a dose-response relationship between HbA1c variability and the risk of DR in patients with T2DM could not be derived from our meta-analysis. Large-scale prospective cohort studies are needed for further investigation. In addition, it remains unknown whether the association between HbA1c variability and the risk of DR in T2DM patients was consistent according to the different severity of DR. Also, only studies published as full-length articles in peer-reviewed journals were included. We acknowledged that excluding the grey literatures may cause potential publication bias. However, low risks of publication biases were retrieved according to the analyses of the funnel plots and Egger's regression tests. Moreover, the potential influences of antidiabetic treatments and concurrent medications on the association between HbA1c variability and DR in T2DM patients are unknown, which should be evaluated in future studies. For example, a previous study suggested that glucose-dependent



▶ **Fig. 3** Funnel plots for the publication bias underlying the meta-analyses; **a**: funnel plot for the meta-analysis with HbA1c variability analyzed with HbA1c-SD and **b**: funnel plot for the meta-analysis with HbA1c variability analyzed with HbA1c-CV.

therapies may be associated with lower within- and between-day glucose variability but similar HbA1c reductions and hypoglycemia duration as compared to glucose-independent strategies in old patients with T2DM [46]. In addition, several clinical studies have also suggested that sitagliptin [47, 48] or dulaglutide [49] may be more effective than sulfonylureas in improving the glucose fluctuation. These findings may highlight the importance of selecting antidiabetic treatments for patients with T2DM, considering the possible additional benefits of reducing glucose variability on the risk of vascular complications. Finally, this is a meta-analysis based on observational studies. Therefore, a causative relationship between high HbA1c variability and increased risk of DR could not be derived based on our findings. Clinical studies should be considered to determine if attenuating HbA1c variability could reduce the risk of DR in patients with T2DM.

Conclusions

In conclusion, results of the meta-analysis suggest that higher HbA1c variability may be associated with an increased risk of retin-

opathy in patients with T2DM. Studies are needed to determine the underlying mechanisms, and to evaluate the impact of reducing glucose fluctuations on the risk of DR in patients with T2DM.

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Conflict of interest

The authors declare that they have no conflict of interest.

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