

Glycated hemoglobin variability: A potential new risk marker for diabetes complications?

Increasing evidence has shown that glycemic instability might contribute to the development of diabetes complications, in addition to the strong relationship between elevated glycemia and diabetes complications risk. In a recent issue of *Diabetes Care*, an analysis of The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study by Penno *et al.*¹ has added to the evidence that variability in glycated hemoglobin (HbA_{1c}) affects albuminuria and albuminuric chronic kidney disease (CKD) phenotypes independently of, or instead of, average HbA_{1c}. On the contrary, diabetic retinopathy mainly depends on the average HbA_{1c}, not variability¹.

Glucose variability refers to multiple fluctuations of glycemia in the same individual within-day or day-to-day, or even over longer periods of time; that is, week-to-week or visit-to-visit. The concept of glucose variability was first introduced in the Diabetes Control and Complications Trial (DCCT), and defined as the standard deviation (SD) of daily blood glucose around the mean from each quarterly visit, even though it proved a weak relationship between glucose variability and diabetes complications². In comparison with the inconsistent association between pre- or postprandial glucose variability and microvascular complication risk, HbA_{1c} variability from visit-to-visit was found to be an independent risk factor for the development of diabetes complications in type 1 diabetes, either solely or in addition to the effect of average HbA_{1c}.

In the current RIACE study, Penno *et al.*¹ retrospectively addressed the asso-

ciations between average HbA_{1c} and HbA_{1c} variability with microvascular complications in Caucasian participants with type 2 diabetes, covering the entire spectrum of renal disease and diabetic retinopathy (Table 1). The RIACE cohort consisted of 15,933 patients from 19 hospital-based diabetes clinics throughout Italy, with three to five HbA_{1c} values in serial visits within a 2-year period before enrolment. In accordance with Tsukuba Kawai Diabetes Registry 2 in Japan³ and the Diabetes Management through an Integrated Delivery System project in Taiwan⁴, the RIACE study added to the fact that HbA_{1c} variability was independently correlated with microalbuminuria and early stages of CKD to the same extent as average HbA_{1c} in patients with type 2 diabetes. Furthermore, they provided the first evidence that HbA_{1c} variability exclusively correlated with macroalbuminuria and the progressive stages of albuminuric CKD instead of average HbA_{1c}. Even though there was substantial data regarding the effect of HbA_{1c} variability on nephropathy risk and the magnitude varied in these studies, the RIACE highlighted the predominant role of HbA_{1c} variability over average HbA_{1c} in accelerating the development of albuminuric nephropathy and reduced estimated glomerular filtration rate.

Patients with more variable HbA_{1c} face a higher risk of microvascular complications, in terms of the frequency and amplitude of HbA_{1c} fluctuation. Previous scientific research attributed the deleterious effect of glucose variability on the kidneys to the metabolic memory induced by repeated exposure to glucose fluctuation. The precise mechanism has not been well determined; however, endothelial dysfunction and oxidative stress were found to be worsened by glucose variability compared with stable hyperglycemia, and could be reversed by

reduction of glucose fluctuation⁵. The RIACE cohort especially emphasized the effect of amplitude of HbA_{1c} fluctuation, as shown by the fact that the risk of progressive nephropathy increased significantly with a higher quartile of HbA_{1c} SD rather than a lower quartile of HbA_{1c} SD¹. Thus, patients lagged in the 'metabolic memory' as a result of frequent HbA_{1c} fluctuation with a large range, and were much more prone to developing severe nephropathy than those with the same average HbA_{1c}, but less variable HbA_{1c}.

In contrast to nephropathy, the association between retinopathy and HbA_{1c} variability was less consistent. Penno *et al.*¹ speculated that the magnitude of HbA_{1c} variability was not high enough to affect the development of diabetic retinopathy, and was masked by average HbA_{1c} and other possible variables related to glycemic exposure, such as diabetes duration and treatments¹. One fact we cannot deny is that type 1 diabetes might have more variable glycemia than type 2 diabetes does. Furthermore, the RIACE cohort with type 2 diabetes showed that increasing average HbA_{1c} was associated with longer diabetes duration, whereas higher HbA_{1c} SD was linked to shorter diabetes duration. In

Table 1 | Risk contribution of visit-to-visit glycated hemoglobin to microvascular diseases in type 2 diabetes

	HbA _{1c} (mean)	HbA _{1c} (SD)
Retinopathy	↑	—
Microalbuminuria	↑	↑
Macroalbuminuria	—	↑
Chronic kidney disease		
Phase 1–2	↑	↑
Phase 3–4	—	↑

HbA_{1c}, glycated hemoglobin.

*Corresponding author. Weiping Jia

Tel: +86-21-64369181-8922

Fax: +86-21-64368031

E-mail address: wpjia@sjtu.edu.cn

Received 4 February 2014; revised 19 February

2014; accepted 20 February 2014

fact, diabetes duration is considered to be the probable strongest predictor for development and progression of retinopathy.

With respect to these facts, there raises the possibility of whether risk reduction of diabetes complications could be achieved by reducing variable HbA_{1c}. Ideal interventions to hyperglycemia aim at lowering hyperglycemia without running the risk of hypoglycemia. Now it might provide benefit beyond simply reducing the risk of hypoglycemia, by avoiding the risk of diabetes complications. To distinguish whether any positive outcomes are as a result of the reduced glycemic variability or just the proved glycemic reduction is still challenging. At least not all diabetes complications are associated with HbA_{1c} variability. More powerful interventional trials should aim to address these remaining questions.

Weiping Jia*

Department of Endocrinology and Metabolism, Shanghai Jiaotong University Affiliated Sixth People's Hospital, Shanghai Clinical Center for Diabetes, Shanghai Key Laboratory of Diabetes Mellitus, and Shanghai Diabetes Institute, Shanghai, China

REFERENCES

1. Penno G, Solini A, Bonora E, *et al.* HbA_{1c} variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. *Diabetes Care* 2013; 36: 2301–2310.
2. Kilpatrick ES, Rigby AS, Atkin SL. The effect of glucose variability on the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 2006; 29: 1486–1490.
3. Sugawara A, Kawai K, Motohashi S, *et al.* HbA_{1c} variability and the development of microalbuminuria in type 2 diabetes: Tsukuba Kawai Diabetes Registry 2. *Diabetologia* 2012; 55: 2128–2131.
4. Hsu CC, Chang HY, Huang MC, *et al.* HbA_{1c} variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study. *Diabetologia* 2012; 55: 3163–3172.
5. Rizzo MR, Barbieri M, Marfella R, *et al.* Reduction of oxidative stress and inflammation by blunting daily acute glucose fluctuations in patients with type 2 diabetes: role of dipeptidyl peptidase-IV inhibition. *Diabetes Care* 2012; 35: 2076–2082.

Doi: 10.1111/jdi.12227