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EDITORIAL

Glycemic Variability, Glycated Hemoglobin, and Cardiovascular Complications: Still a Dilemma in Clinical Practice

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Key Summary Points

HbA1c remains a very important laboratory measurement for patients with diabetes, although its sole use cannot be recommended for a comprehensive evaluation of their glycemic control.

Proper management of glycemic variability contributes to improve the cardiometabolic outcome in patients with type 2 diabetes mellitus regardless of HbA1c levels.

We highly recommend the evaluation of glycemic variability in clinical practice, together with the usual measurements of HbA1c and fasting glucose.

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EDITORIAL

In the present issue of *Advances in Therapy*, Li et al. [1] have investigated the relationship between achieving glycemic targets and glycemic variability in Chinese patients with type 2 diabetes mellitus (T2DM). Despite some limitations due to the nature of their post hoc analysis, the authors did not find a significant association in reaching HbA1c target and glycemic variability. This finding seems to support the hypothesis that proper management of glycemic variability may contribute to improve the cardiometabolic outcome in patients with T2DM regardless of HbA1c [2]. Although the measurement of HbA1c is suggested by international scientific guidelines as a useful marker to evaluate glycemic control and with prognostic value for diabetes complications [3],

some authors have discussed the inadequacy of the use of HbA1c as the sole marker, since its measurement in isolation can be even misleading [4].

Currently, HbA1c levels are well managed in patients with diabetes on medications with low hypoglycemia risk, which is something quite common in our days with the wide use of dipeptidyl peptidase 4 (DPP4) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1RAs), and sodium-glucose co-transporter 2 inhibitors (SGLT2i), as well as the new types of basal insulin analogues [3]. Yet, a large body of evidence suggests that glycemic variability should be also taken into account, beyond HbA1c [4]. Indeed, glycemic variability can not only be a dangerous condition for the cardiovascular system [2] but it is also associated with increased risk of hypoglycemia, which is strictly linked to adverse cardiovascular outcome and all-cause mortality [2]. Therefore, no further delay is allowed for the management and treatment of glucose variability, in order to ensure effective prevention of diabetic complications [5].

The mechanisms involved in the genesis and severity of adverse clinical outcomes due to glycemic variability have been investigated over the years and, overall, a direct role of glycemic variability in tissue damage has been highlighted, with oxidative stress as the key player in producing damage to endothelial cells [6]. Some authors have shown the relationship between daily and day-to-day glycemic variability and increased oxidative stress in patients with T2DM [7], as well as demonstrating that oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in patients with T2DM [8]. These preliminary observations were then completed with the finding of a strong association between glycemic variability and markers of vascular damage, including oxidative low-density lipoproteins (LDL) [9].

Indeed, diabetic dyslipidemia is usually formed by alterations in the quality rather than the quantity of LDL [10], with increased levels of denser LDL particles with smaller size, and greater atherogenicity, due to reduced LDL receptor affinity, higher susceptibility to oxidation, and greater arterial entry and retention [11]. Small, dense LDL particles are prevalent in several categories of patients at high cardiovascular risk, including T2DM and gestational diabetes [12–15], and have been recognized as an independent risk factor for cardiovascular diseases [11], being a key factor for the development and progression of atherosclerosis and endothelial dysfunction, which both amplify the risk of cardiovascular events [16]. Some inflammatory cytokines, such as resistin, are closely associated with small, dense LDL and seem to play a role in diabetes and cardiovascular diseases [17].

Of interest, some novel antidiabetic medications have shown favorable effects on glycemic variability [18], with interesting data coming from the use GLP-1RAs [19, 20] and SGLT-2i [21]. This is of great clinical importance, since the use of these novel antidiabetic agents in patients with T2DM results in glycemic control, metabolic benefit as well as a positive cardiovascular outcome [22]; on this basis, GLP-1RAs and SGLT2i are recommended as first-line antidiabetic therapies by current guidelines issued by both diabetologists and cardiologists [23]. In addition, some GLP-1RAs improve oxidative stress, endothelial dysfunction, subclinical atherosclerosis, and atherogenic small dense LDL [24–27], all of which seems to be key mechanisms for the tissue damage induced by glycemic variability, as discussed above.

In conclusion, HbA1c remains a very important laboratory measurement for patients with diabetes, although its sole use cannot be recommended for a comprehensive evaluation of their glycemic control; indeed, increasing evidence suggests the need to monitor not only HbA1c and fasting glucose but also postprandial glucose and glycemic variability [4]. Since the assessment of glycemic variability significantly contributes to proper management and treatment of patients with diabetes and also to prevent future complications [5], we highly recommend the evaluation of glycemic variability in clinical practice together with the usual measurements of HbA1c and fasting glucose.

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