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# The evolving frontier of diabetes therapy: The renaissance of glycemology

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ABSTRACT

It was previously proposed that diabetes could be a "cardiovascular disease". This concept was based on evidence showing that controlling hypertension and dyslipidemia could be more effective than controlling hyperglycemia. At that time it was concluded that the real need to focus on reaching optimal glycemic control had lost its appeal. However, the concept of glycemic control was strictly correlated to levels of glycated hemoglobin (HbA1c), the integrated measure of mean glycemia over the previous 2–3 months, while recent evidence suggests that the concept of hyperglycemia has profoundly changed, and it is more appropriate to speak of different kinds or aspects of hyperglycemia. A modern, updated approach to glycemic control in people with diabetes, in fact, must focus not only on reaching and maintaining optimal HbA1c levels as soon as possible, but to obtain this result by reducing postprandial hyperglycemia and glycemic variability, while avoiding hypoglycemia.

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Hyperglycemia is the hallmark of all forms of diabetes, including the most common, type 1 (T1D) and type 2 (T2D), and the pathogenetic determinant of diabetes-specific microvascular disease retinopathy, nephropathy, and neuropathy. Moreover, hyperglycemia is also a major contributor to the increased risk of cardiovascular disease (CVD), including myocardial infarction, stroke, and limb ischemia, associated with diabetes. Landmark intervention trials, such as the DCCT/EDIC in T1D and the UKPDS in T2D have demonstrated that intensive therapy, aiming at correcting, or at least mitigating hyperglycemia is effective in preventing or delaying microvascular complications, while its effect on reducing CVD risk is less obvious and requires longer to become assessable [1,2]. Years ago, from a perhaps biased cardiovascular perspective, this led to the assumption that diabetes itself was a "cardiovascular disease" [3], implicitly minimizing the role of hyperglycemia as causative factor of CVD and the relevance of its control for reducing CVD risk and improving patient survival. The concept of marginal contribution of glucose control on patient CVD outcome has been further strengthened by: (a) evidence that control of hypertension and dyslipidemia, which cluster with hyperglycemia in most patients with type 2 diabetes, is quantitatively more effective than control of hyperglycemia in the prevention of CVD [4]; and (b)

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disappointing results from three large trials conducted in the 2000s (ACCORD, ADVANCE, VADT) which failed to demonstrate that tight glucose control is able to reduce CVD risk in patients with T2D [5], even with an increased mortality in ACCORD: an increase of 22% in the hazard ratio for all-cause mortality and 35% for cardiovascular mortality [6]. Based on these observations, the temptation to focus on reaching an optimal glucose control, at least in T2D, lost its appeal.

However, subsequent reflections and analyses indicated that, individually, those trials were relatively underpowered due to low incidence of events, short duration of follow up, and relatively small differences in glucose control between intensive and control intervention groups [7]. In fact, a meta-analysis on these and two other major randomized controlled trials (UKPDS, PROactive) showed that intensive glucose control had cardiovascular benefits, although not affecting overall mortality [8]. Moreover, strategies of intensive glucose control in patients with advanced T2D with traditional agents, including insulin and sulfonylurea, might have been incorrect, especially with regard to severe hypoglycemia, which was higher in patients with tightly controlled glucose and was independently associated with higher CVD risk [9]. Therefore, the incidence of hypoglycemia may counterbalance the potential benefit of intensive glucose control, on one side directly suggesting therapeutic approaches with lower risk of hypoglycemia, and, on the other, accurate glucose monitoring in patients with diabetes.

Glycated hemoglobin (HbA1c), the integrated measure of mean glycemia over the previous 2–3 months, is the most important marker of glucose control and is commonly used to evaluate and correct diabetes treatment. Although several studies have established the relationship between average glucose and HbA1c levels [10], information on the glucose daily profile deriving from self-monitoring of blood glucose (SMBG) or, when available, continuous glucose monitoring (CGM), is essential for adequate diabetes management.

The inadequacy of the use of HbA1c as sole marker of glucose control also emerged recently from a Swedish nationwide T1D registry-based report, where patients with an optimal HbA1c of $\leqslant$6.9% had a twofold higher risk of death from any cause or from cardiovascular causes compared with controls without diabetes [11]. Since T1D is a model of pure hyperglycemic disease, with no or marginal contribution by obesity, hypertension, or hypercholesterolemia typical of type 2, the increased risk of death in patients with good glycemic control seems, at a first glance, unexplained. However, since HbA1c integrates an average, it is crucial to dissect what this average reflects and how the concept of optimal glucose control can evolve and be revised.

In fact, the concept of hyperglycemia has recently changed, and it is more appropriate to consider the different kinds and facets of hyperglycemia. Postprandial hyperglycemia (PPH) has been proposed as an independent risk factor for CVD [12]. This hypothesis has still not been completely demonstrated; however, there is no doubt that the control of PPH is mandatory in order to achieve optimal HbA1c values [12]. Glucose variability is also emerging as an independent risk factor for CVD, both in people with and without diabetes [13,14]. The concept of glucose variability is composite, since it introduces the notion that multiple fluctuations of blood glucose in the same individual could be more harmful than either a distinct episode of acute hyperglycemia, or a condition of chronic sustained hyperglycemia [13,14]. To define the concept of glucose variability, a PubMed term search for "glucose variability" was carried out and found almost 3000 hits [14]. The literature generated on this subject is extremely heterogeneous, with many different concepts grouped together under the same term. One concept refers to the between-day variability of fasting glycemia; a second to postprandial glycemia peaks; a third to the variability of HbA1c over time; a fourth to hypoglycemic episodes; and finally, the most common, includes within-day glucose variability, which is, in turn, evaluated by means of blood glucose values obtained via SMBG or CGM. In short, the term "glucose variability" should always be defined by identifying the specific concept that it refers to [14].

Moreover, any episode of hypoglycemia, recurrent or isolated, are also components of glucose variability: in this respect, in addition to the known role of hypoglycemia as a risk factor for CVD [15], is worth noting that hyperglycemia following recovery after hypoglycemia has an ischemia–reperfusion like effect, acting, in turn, as a further risk factor for CVD [16,17].

HbA1c, integrating in a single marker the average of all these variables, cannot also incorporate the possible further burden deriving from hypoglycemic events, recovered or not with hyperglycemia, PPH, and, in general, wide glucose fluctuations compared with a comparable HbA1c value reflecting the same average, but with fewer of these components. This might be particularly true in the presence of optimal values of HbA1c, where the risk associated with the extremes can equipoise the benefits of good average glucose levels. This could explain the lack of benefit of tight versus standard glucose control in T2D with relatively high baseline CVD risk, as well as the persistent excess mortality in T1D despite good glucose control.

It is clear in this scenario that HbA1c represents only one aspect of glycemic control and that today the management of glycemia appears more challenging than in the past. A modern, updated, approach to glycemic control in people with diabetes, in fact, must focus not only on reaching and maintaining the best HbA1c level, but to obtain this result by reducing PPH and glycemic variability, avoiding hypoglycemia. Finally, to be effective, optimal glycemic control must be implemented as soon as possible, in order to avoid the appearance the phenomenon of "metabolic memory" [18]. The concept of the "metabolic memory", that is, of diabetic vascular stresses persisting after glucose normalization, has been supported by data from the laboratory as well as from the clinic [18], both in T1D (DCCT/EDIC) [1], and T2D (UKPDS) [2].

Today, this challenge can be faced via two avenues: better therapies and better glucose measurements. The ideal treatment for diabetes should be safe, effective, simple, affordable, and personalized in order to reach the set targets. Over the last decade we became familiar with entirely new classes of anti-diabetes agents: dipeptidyl peptidase 4 inhibitors, glucagon-like peptide-1 receptor agonists, and basal insulins

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