ONLINE EXCLUSIVE

Glycemic variability: Too often overlooked in type 2 diabetes?

Look beyond the HbA1c average, and consider introducing insulin earlier in the disease process.

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PRACTICE RECOMMENDATION

❒ *Consider evaluating 24-hour variability in glucose levels with patients' self-monitoring glucose meters (in addition to monitoring glyco-sylated hemoglobin [HbA1c] levels at regular intervals).* Ⓒ

❒ *If glycemic goals are unmet 2 to 3 months after initiating treatment with exercise and diet or with oral agent monotherapy, consider starting insulin therapy.* Ⓒ

Strength of recommendation (SOR)

Ⓐ Good-quality patient-oriented evidence

Ⓑ Inconsistent or limited-quality patient-oriented evidence

Ⓒ Consensus, usual practice, opinion, disease-oriented evidence, case series

Though we have the knowledge and the means to reduce complications of type 2 diabetes mellitus (T2DM), most patients may not be reaching all the glycemic goals necessary to achieve optimal risk reduction.[1] Maintaining an acceptable level of glycosylated hemoglobin (HbA1c) is one of the important glycemic goals. But that measurement is an average of glucose levels occurring over the prior 3 months. Regardless of a given HbA1c measurement, an emerging body of evidence supports the presumption that glycemic variability over each 24-hour cycle is an independent risk factor for vascular complications.[2-15]

In this article, I review the literature pertaining to the risk associated with glycemic variability and to the benefit in correcting it. I also review the comparative outcomes achievable with normal human insulin and insulin analogs, as well as the advisability of starting insulin earlier in the management process.

Glycemic variability increases vascular risk independently

HbA1c, considered the gold standard for monitoring glycemic control in patients with T2DM, is an average of the full range of glucose values in the preceding 3 months, including fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG) levels. Studies have linked lowering HbA1c to reducing the risk and progression of micro- and macrovascular complications associated with diabetes.[16,17] But evidence shows that other glycemic values are also important.

The Diabetes Control and Complications Trial (DCCT) was a landmark study in which patients with type 1 diabetes mellitus who received targeted intensive insulin therapy experienced delayed onset and slowed progression of microvascular complications compared with those who received conventional insulin treatment.[16] Interestingly, this study also reported that patients randomized to receive conventional insulin treatment did not exhibit a reduction in the

risk of progression of microvascular disease despite having HbA1c values comparable to those in the intensive-treatment group. One hypothesis is that glucose excursions occurred more frequently in the conventionally treated group, which received fewer daily insulin injections.[5]

Acute glucose fluctuations during the postprandial period trigger oxidative stress and are more predictive of atherosclerosis development than are FPG or HbA1c[6,7] (see "Implications of glycemic variability" below). This suggests that therapy for patients with T2DM should not only target HbA1c as a long-term goal, but also aim to avoid acute glucose fluctuations as an immediate goal. Several studies have shown that postprandial hyperglycemia is an independent risk factor for vascular complications in patients with T2DM.[2,7-9,12,14,15]

▌**Evidence of increased vascular risk with glycemic variability.** The Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe study (DECODE) followed more than 25,000 patients for more than 7 years and found that increased mortality was more closely associated with increased 2-hour PPG levels than with FPG.[14] In the Framingham Offspring Study, Meigs et al[9] reported that, in nondiabetic subjects, an elevated glucose level 2 hours after an oral

> **In a study with 25,000 patients, increased mortality was more closely associated with 2-hour postprandial glucose levels than with fasting plasma glucose levels.**

Implications of glycemic variability

Normal physiologic insulin secretion prevents glucose fluctuations in healthy adults. In patients with diabetes, abnormalities in insulin secretion are part of the pathophysiologic process, resulting in chronic sustained hyperglycemia and acute daily fluctuations in glucose levels. These glycemic disorders are associated with a state of increased oxidative stress and possible subsequent development of vascular complications.
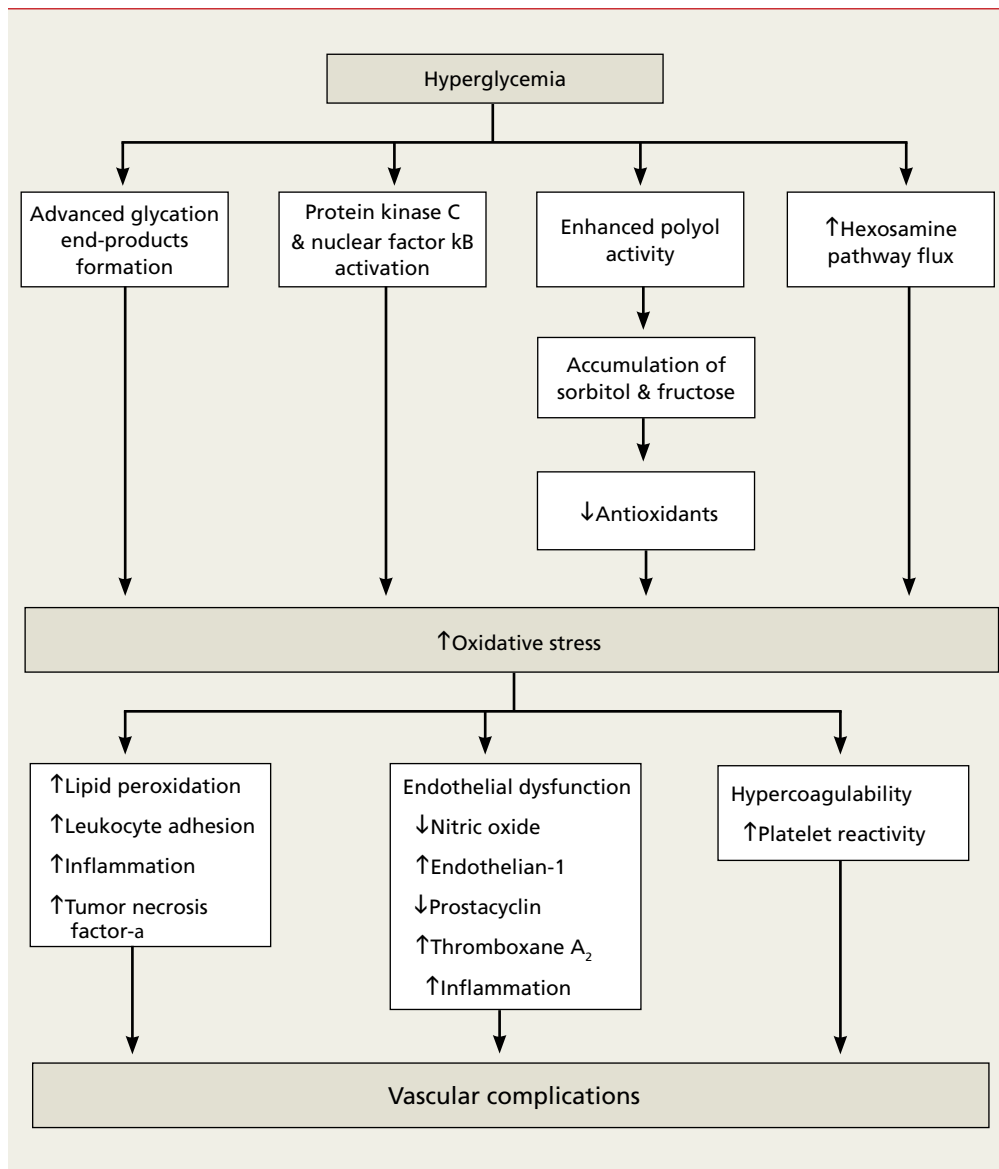
Cellular response to hyperglycemia. Oxidative stress, the imbalance between production of reactive oxygen species and the ability to eliminate them, is central to the pathogenesis of cardiovascular complications of diabetes, including accelerated atherosclerotic macrovascular disease (FIGURE 1). Both insulin resistance and hyperglycemia are implicated in the pathogenesis of these complications.[65,66] Hyperglycemia is hypothesized to induce vascular injury via at least 4 biochemical pathways: enhanced polyol activity leading to sorbitol and fructose accumulation; increased formation of advanced glycation end products; activation of protein kinase C and nuclear factor kB; and increased hexosamine pathway flux.[67] Endothelium activation is a pro-inflammatory, proliferative, and pro-coagulatory setting, ultimately leading to arterial narrowing and susceptibility to atheroma deposition. Hyperglycemia can also induce alterations in the coagulation system, resulting in increased thrombosis.[68]

Association of glycemic variability with oxidative stress. Macrovascular complications, particularly cardiovascular disease, contribute significantly to the increased morbidity and mortality with diabetes.[24] Oxidative stress has been implicated as a major factor in the development of these complications.[66-68] Other cell-culture evidence suggests that normal protective mechanisms of oxidative stress are impaired by chronic hyperglycemia. When exposed to intermittent glycemic variability, cells have exhibited more pronounced toxicity.[69,70] Risso et al[71] further established that variability in glycemic control resulted in more endothelial cell damage than did chronic sustained hyperglycemia.

Despite the experimental evidence that suggests glycemic variability is associated with increased risk of vascular complications, there are limited clinical data establishing glycemic variability as an independent predictor of these complications. Monnier et al[72] provided data in patients with type 2 diabetes mellitus (T2DM) to support the concept of acute glucose fluctuations as a more important trigger of oxidative stress than chronic hyperglycemia. If these data are confirmed in larger clinical trials, a monitoring paradigm for patients with T2DM could include increased focus on preventing glucose excursions in addition to reducing HbA1c.

FIGURE 1

How oxidative stress secondary to hyperglycemia leads to vascular complications in diabetes[66-68]

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                        ┌─────────────────────┐
                        │    Hyperglycemia    │
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| Advanced glycation end-products formation | Protein kinase C & nuclear factor kB activation | Enhanced polyol activity | ↑Hexosamine pathway flux |

Accumulation of sorbitol & fructose

↓Antioxidants

↑Oxidative stress

↑Lipid peroxidation
↑Leukocyte adhesion
↑Inflammation
↑Tumor necrosis factor-a

Endothelial dysfunction
↓Nitric oxide
↑Endothelian-1
↓Prostacyclin
↑Thromboxane A$_2$
↑Inflammation

Hypercoagulability
↑Platelet reactivity

Vascular complications

> **Having patients take glucose readings at various times of the day can give a clearer picture of glycemic variability than just a postprandial plasma glucose reading.**

challenge increased the relative risk for cardiovascular disease by up to 40%, independent of fasting hyperglycemia.

■ **Mixed outcomes with HbA1c reduction only.** Macrovascular risk reduction with intensive HbA1c management was not apparent in 3 recent studies—Action to Control Cardiovascular Risk in Diabetes (ACCORD),[18] Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE),[19] and Veterans Affairs Diabetes Trial (VADT).[20] The ACCORD study, in fact, showed an increase in cardiovascular events in the intensively managed group (HbA1c target <6.0%). Indeed, previous studies had suggested an association between fasting hypoglycemia and poor cardiovascular outcomes.[3,4] Retrospective subanalysis of the ACCORD study suggested that patients with poorer glycemic control had a greater

TABLE 1

Aim to reach 3 glycemic goals in treating type 2 diabetes mellitus

	ADA	AACE
Fasting blood glucose (mg/dL)	90-130	<110
Postprandial plasma glucose (mg/dL)	<180	<140
HbA1c (%)	<7*	≤6.5

*Recommended "in general"; however, the guideline indicates that for "the individual patient," HbA1c should be as close to normal (<6%) as possible without causing hypoglycemia.

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; HbA1c, glycosylated hemoglobin.

Sources: ADA, http://care.diabetesjournals.org/content/33/Supplement_1/S11/T11.expansion.htm; AACE, http://www.aace.com/pub/pdf/guidelines/DMGuidelines2007.pdf.

> **Rapid-acting insulin analogs can be taken closer to mealtime, likely giving patients tighter postprandial glucose control and reducing glycemic excursions.**

risk of hypoglycemia independent of HbA1c values, and that patients who had difficulty reaching lower HbA1c levels may have had poorer cardiovascular outcomes.[21]

The apparent absence of a reduction in macrovascular events in the ACCORD, ADVANCE, and VADT studies also suggests an additive effect of nonglycemic risk factors that frequently accompany diabetes—ie, hypertension, hyperlipidemia, and hypercoagulability/pro-inflammatory states.

Long-term follow-up in the United Kingdom Prospective Diabetes Study (UKPDS) showed ongoing risk reduction for both microvascular and macrovascular complications.[22] A separate meta-analysis showed a significant 10% reduction in cardiovascular events with intensive glycemic control when data were combined from the ACCORD trial, ADVANCE trial, VADT, and the UKPDS.[23]

An improvement in long-term outcomes for patients with T2DM might be expected when initiating a targeted, intensified, multifactorial interventional regimen to reduce not only HbA1c, but also glucose variability. The STENO-2 trial showed that a targeted multifactorial treatment regimen in patients with T2DM could decrease long-term vascular complications.[24]

▌**Consider assessing true variability in your patients.** Because postprandial glucose levels alone may not equate to overall glycemic variability, you may want to ask select patients to take readings with their glucose meters at various times of the day across several days to get a more accurate picture.[5]

Following through with targeted, intensified management

Consider the following treatment goals for patients with T2DM: (1) lowering HbA1c levels; (2) lowering fasting blood glucose levels; (3) minimizing glycemic variability, including postprandial glucose excursions. **TABLE 1** lists the values that the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have assigned to these glycemic-control goals.

In addition to managing glycemic levels, reducing risk of cardiovascular disease in T2DM involves aggressive interventions, as needed, to correct blood pressure and lipid levels.[24,25]

Challenges to achieving glycemic control

Despite current recommendations for more aggressive management of patients with T2DM,[25] estimates are that as many as 60% of patients with T2DM do not achieve glycemic targets, and, as the disease progresses, many of the available treatment options fail to sustain levels previously reached.[1,26,27]

A shortcoming of older treatment strategies still in use is the slow transition to more effective therapy, resulting in long periods of inadequate glycemic control.[1] Brown et al[27] found that patients receiving monotherapy with either a sulfonylurea or metformin had HbA1c levels >8% for a mean of 20 months and 14 months, respectively, before treatment was changed. Current recommendations call for treatment changes within 2 to 3 months of initiation of therapy if the HbA1c goal is not reached.[27-29]

▌**Turning to insulin earlier.** Insulin is most effective for lowering HbA1c and delaying subsequent complications related to diabetes; however, there is often reluctance to using it early in diabetes management. Consequently, by the time insulin therapy is started, many patients will have had unacceptable glycemic levels for 10 years or more and may already be developing complications.[27] And, as noted, the HbA1c level is an average measurement that does not detect glycemic variability. Continuous glucose monitoring will

TABLE 2

Pharmacokinetic properties giving insulin analogs an advantage over regular insulin[46-50]

Insulin preparation	Onset of action	Peak action	Duration of action
Short-acting			
Regular	30-60 minutes	2-3 hours	8-10 hours
Lispro	5-15 minutes	30-90 minutes	4-6 hours
Aspart	5-15 minutes	30-90 minutes	4-6 hours
Glulisine	20 minutes	90 minutes	5.3 hours
Long-acting			
NPH	2-4 hours	4-10 hours	12-18 hours
Glargine	2-4 hours	Relatively flat	Up to 24 hours
Detemir	1-2 hours	Relatively flat	Up to 24 hours

NPH, neutral protamine Hagedorn.

likely lead to more responsive adjustments in treatment regimens and to improved quality of care for patients with T2DM.

Insulin has many beneficial effects

Insulin exerts an anti-inflammatory effect by reducing the increase in C-reactive protein and serum amyloid A.[30] It also partially restores insulin-stimulated endothelial function,[31] facilitates vasodilation by increasing nitric oxide production,[32] and improves fibrinolytic profiles.[33] Early initiation of insulin therapy can increase peripheral insulin sensitivity and preserve beta cell function.[34-36]

When oral agents have failed, insulin can significantly improve patients' beta cell function,[34,35,37] and short periods of insulin therapy in patients newly diagnosed with T2DM may even set the foundation for better long-term control.[38,39]

But not all insulin is alike

Ideally, insulin therapy should mimic physiologic insulin secretion. However, conventional human insulin products fail to do so because of their suboptimal pharmacodynamic profiles. With recombinant DNA technology, molecular modifications of the human insulin molecule have overcome some of the limitations of conventional human insulin products.

Unfortunately, many practitioners still hold insulin in reserve until combination therapy with oral agents has failed, possibly resulting in years of suboptimal glycemic control. Newer strategies recommend earlier initiation of insulin—ie, once diet and exercise fail, or when treatment with 1 oral agent fails. The development of insulin analogs is a significant milestone on the road to achieving improved outcomes for patients with T2DM.
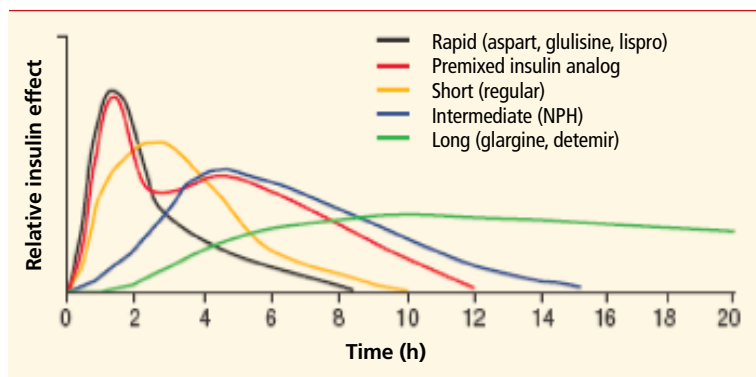
Rapid-acting agents

Compared with regular human insulin, newer rapid-acting insulin analogs may improve glycemic control when used at mealtimes. However, due to their shorter half-lives, these insulin analogs require augmentation with basal insulin to control hyperglycemia between meals and during the night.

Insulin lispro was the first commercially available rapid-acting insulin analog, introduced in 1996. This agent differs from human insulin by an inversion of amino acid residues in positions 28 and 29 of the insulin B-chain. Inversion prevents the formation of hexamers and dimers that tend to diffuse more slowly, thereby facilitating a rapid uptake of the insulin analog into blood and tissues.[40,41] The second such agent, marketed in 2000, was insulin

FIGURE 2

Pharmacokinetic profiles of human insulin and insulin analogs

Adapted from: Burton S. *J Fam Pract*. 2006;55(12 suppl):S10-S17.

aspart, in which aspartic acid replaces proline at position 28 of the B-chain of human insulin.[41,42] The most recent rapid-acting analog is insulin glulisine, in which lysine replaces asparagine near the N-terminus of the B-chain, and glutamic acid replaces lysine near the C-terminus of human insulin.

The molecular changes made in creating these analogs allows them to dissociate quickly into monomers that are absorbed rapidly and achieve faster peak levels compared with regular human insulin.[41,42] These changes do not, however, interfere with the analogs' ability to bind to the insulin receptor.[43,44]

▌**Dosing considerations.** Absorption of regular human insulin is not sufficiently rapid at mealtimes to control prandial glucose levels.[45] Therefore, it is essential to give regular insulin 30 to 60 minutes before meals. For patients who have erratic daily schedules, adhering to this sort of routine can be difficult. But even if scheduling is not a problem, the prolonged duration of action of human insulin can predispose patients to hypoglycemia. Moreover, absorption of regular insulin can vary dramatically from day to day.[46,47]

The insulin analogs correct the pharmacokinetic and pharmacodynamic deficiencies of regular insulin, producing plasma profiles that more closely simulate normal, physiologic meal-stimulated insulin release.[48-50] The 3 rapid-acting agents (aspart, glulisine, lispro) have very similar onset and duration

of action, with peak effect occurring close to injection time (**TABLE 2** and **FIGURE 2**).[48-50]

▌**Advantages of rapid-acting agents.** These agents can be administered closer to meals, giving patients more flexibility and likely tighter postprandial glucose control, with reductions in glycemic excursions. Another advantage is the ability to better match insulin dose to anticipated carbohydrate intake, affording better postprandial control.[51-53] Rapid-acting analogs also result in fewer episodes of hypoglycemia. In a meta-analysis of 2576 patients, hypoglycemic events occurred 25% less often with insulin lispro compared with regular human insulin in patients with type 1 diabetes mellitus (T1DM).[52] In clinical trials, insulin aspart and insulin glulisine have also caused fewer hypoglycemic events compared with regular human insulin.[51-53]

Long-acting agents

Basal, or long-acting, insulins are important for maintaining normoglycemia over 24 hours. Neutral protamine Hagedorn (NPH) insulin reaches its peak effect 4 to 10 hours after injection, and its total effect lasts only 12 to 18 hours. NPH is therefore often dosed twice daily. Absorption of NPH can vary significantly, causing day-to-day blood glucose fluctuations.[46,47] Therefore, this agent's activity does not closely resemble normal physiologic basal insulin secretion.

The newer long-acting insulin analogs—insulin detemir and insulin glargine—were designed to more closely replicate normal physiologic basal insulin secretion. Insulin glargine was first to reach the market, in 2001. It contains glycine instead of asparagine in the alpha-chain and 2 arginine residues at the C-terminus, and the addition of zinc enhances the aggregation and slow release at a neutral pH. Insulin glargine precipitates in the subcutaneous tissue, which slows its absorption and results in a relatively flat insulin plasma profile and extended action.[54,55] Insulin detemir is a combination of the original insulin molecule and a saturated fatty acid (myristic acid). Insulin detemir is designed to bind albumin (98% albumin-bound in circulation) through this fatty acid chain in the plasma after injection, resulting in an extended plasma profile.[54,56] Insulin glargine and

NPH form crystalline depots, but detemir is soluble and the subcutaneous depot remains in a liquid state; this may account for differences in absorption variability.[56]

▌**Advantages of the long-acting insulin analogs.** Compared with conventional basal insulin such as NPH, the analogs have a prolonged duration of action (up to 24 hours) without pronounced peaks, permitting once-daily dosing in many patients (**TABLE 2** and **FIGURE 2**).[46,47,50,55] The pharmacodynamic and pharmacokinetic properties of the long-acting agents make them less likely than NPH to cause nocturnal and overall hypoglycemia, a benefit that has been observed in several clinical trials.[57-61]

▌**Comparative clinical trials evaluating glycemic variability.** Both of the long-acting analogs have shown lower within-subject variability in blood and plasma glucose measurements when compared with NPH.[62-64] In head-to-head comparisons of the analogs in glucose clamp studies, insulin detemir has demonstrated less within-subject variability of blood glucose levels than insulin glargine, in patients with T1DM or T2DM.[56,64] In clinical practice, different patients may have better results with one of these basal insulins as opposed to the other, and treatment choices will need to be tailored to the individual patient. **JFP**

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> Long-acting insulin analogs stay active up to 24 hours without pronounced peaks, permitting once-daily dosing in many patients.

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