

Reducing Oxidative Stress in Patients with Type 2 Diabetes Mellitus: A Primary Care Call to Action

Jeff Unger, MD

Catalina Research Institute, Chino, California

ABSTRACT

Background: Oxidative stress is believed to be the primary cause of the microvascular and macrovascular complications of type 2 diabetes mellitus (DM).

Objective: This paper examines the evidence linking oxidative stress with long-term complications of type 2 DM and explores methods to minimize its effect.

Methods: A literature search was performed to identify relevant studies for this review. Articles published in English from 2000 to 2008 were identified through searches of PubMed, *Diabetes Care*, and Google using the search terms *oxidative stress*, *postprandial hyperglycemia*, *ACCORD Trial*, and *endothelial cell dysfunction*.

Results: The literature search identified 423 articles. Although chronic hyperglycemia can be effectively monitored and targeted using glycosylated hemoglobin concentrations, postprandial glucose levels are also important. Postprandial glucose excursions are exhibited by almost all patients with type 2 DM and are independent risk factors for cardiovascular morbidity and mortality. Furthermore, glucose fluctuations during the postprandial period elicit more oxidative stress than chronic, sustained hyperglycemia and can lead to endothelial dysfunction, vascular inflammation, and microvascular complications. In turn, endothelial dysfunction has been implicated in the development of vascular pathologies such as atherosclerosis. Pharmacologic interventions (eg, rapid-acting insulin analogues that target postprandial glucose excursions) reduce oxidative stress and vascular inflammation and improve endothelial dysfunction.

Conclusions: Given the important role of oxidative stress in the development of complications of type 2 DM, physicians should consider methods to reduce oxidative stress that may occur during both acute (postprandial) and chronic hyperglycemia. One critical aspect is to reduce postprandial glucose levels to <180 mg/dL while lowering fasting glucose levels to <110 mg/dL. By coaching patients to reach these goals, physicians and other health care professionals can minimize the risk of long-term complications of type 2 DM. (*Insulin*. 2008;3:176–184) © 2008 Excerpta Medica Inc.

Key words: type 2 diabetes, oxidative stress, endothelial dysfunction, postprandial hyperglycemia.

INTRODUCTION

The effects of chronic hyperglycemia, hyperlipidemia, and hypertension in patients with diabetes mellitus (DM) places these individuals at high risk for microvascular and macrovascular complications. Approximately 80% of patients with type 2 DM will succumb to cardiovascular complications such as stroke, peripheral arterial disease, and heart disease.¹ Although DM carries a 1.5- to 4.5-fold risk of cardiovascular mortality,² the microvascular complications of DM (eg, retinopathy, nephropathy, and neuropathy) can have devastating effects on patients' quality of life.

Long-term outcomes are influenced by both the severity of hyperglycemia and the length of time that susceptible cells are exposed to elevated glucose levels. Postinfarction mortality is significantly higher in the presence of acute hyperglycemia than with infarctions that occur when glucose levels are physiologic.³ Stroke patients who present to

the emergency department with glucose levels >160 mg/dL suffer greater neurological sequelae and have a higher mortality rate than stroke patients who are euglycemic.^{4,5}

The microvascular and macrovascular complications of DM are believed to be caused by a process known as *oxidative stress*. Intracellular oxidative stress occurs when the production of reactive oxygen species (byproducts of normal metabolism) exceeds the capacity of the cell's antioxidants to neutralize them.⁶ Endothelial cells chronically exposed to oxidative stress favor the induction of specific long-term complication pathways. Oxidative stress associated with hyperglycemia can be limited by maintaining optimal glycemic control with appropriate oral and injectable agents. By efficiently managing exposure to both chronic and acute postabsorptive hyperglycemic excursions, health care providers can coach patients to maintain "physiologic glycemia" and minimize long-term complications.

The purpose of this article was to examine the evidence linking oxidative stress with long-term complications of type 2 DM and explore methods to minimize its effects.

METHODS

A literature search was performed to identify relevant studies for this review. Articles published in English from 2000 to 2008 were identified through searches of PubMed, *Diabetes Care*, and Google using the search terms *oxidative stress*, *postprandial hyperglycemia*, *ACCORD Trial*, and *endothelial cell dysfunction*.

RESULTS

The literature search identified 423 articles.

Practical Tools Needed for Successful Diabetes Management

Although easier said than done, physicians must understand that, when provided with the appropriate tools, most patients will become successful at diabetes self-management. Before labeling a patient with diabetes as being “noncompliant,” clinicians should consider the following scenario: How many clinicians could check their blood glucose levels 4 times each day, determine how much insulin to use based on each meal’s carbohydrate content and their premeal glucose values, and time the injection of insulin properly? Before injecting insulin, the insulin user would have to know all of the information presented in **Table 1**⁷⁻⁹ to maintain postabsorptive glycemic control.

Table 1. Physiologic regulation of postprandial hyperglycemia for patients with diabetes mellitus.

Regulating Factor	Comment	References
Timing of injection	Rapid-acting insulin analogues and inhaled insulin should be administered 10 to 15 minutes before meals. (Glulisine may be given up to 20 minutes after meals.) Exenatide may be administered within 60 minutes of starting a meal. Pramlintide should be injected immediately before a major meal (>250 kcal or containing >30 g of carbohydrate).	7,8
Nutritional content and quantity of food to be eaten	A higher fat content will delay the absorption of carbohydrates as well as the corresponding rise in postabsorptive glucose levels. This will, of course, necessitate a different dosing strategy for the prandial insulin. Prior experience with similar mealtime insulin dosing is important. “What happened last time I administered this amount of insulin for this type of meal under similar circumstances?”	9
Dose correction	Time and amount of previous insulin bolus. If given within 4 hours, it may be necessary to reduce the current dose by at least 20% to avoid insulin stacking and hypoglycemia. Timing of anticipated exercise. If exercise is planned within 2 hours of eating, the mealtime bolus should be reduced by 50%.	7
Rate of gastric emptying	If gastric emptying is delayed and a rapid-acting insulin analogue is administered as usual (10–15 minutes before eating), the patient will experience a mismatch between rapid insulin absorption and pharmacologic action with a delayed increase in postabsorptive glucose levels. This translates into erratic glucose control, typically a hypoglycemic event occurring soon after the patient completes the meal, followed by significant postabsorptive hyperglycemia 2 to 3 hours after the injection is given.	7
Counterregulatory hormones	Hepatic glucose production (HPG) is minimized by endogenous basal insulin secretion at the rate of 1 unit per hour. Insulin resistance and β -cell death increase HPG, which results in elevated fasting glucose levels. Patients who start the day with fasting hyperglycemia are likely to continue having postprandial elevations as well. Glucagon is secreted from pancreatic α -cells in response to impending hypoglycemia. Glucagon converts the liver stores of glycogen into glucose as an immediate energy source. Glucagon levels are normally regulated by endogenous insulin. However, as insulin levels decline, glucagon levels increase, especially in the postprandial and postabsorptive phases, causing significant hyperglycemia.	8

Clinicians should consider the mind-set of these patients and understand that these individuals do not have a functioning pancreas. As such, their brains become a surrogate pancreas. What is my current blood glucose level? How much insulin do I require to normalize my hyperglycemia before eating? How many grams of carbohydrates will I be consuming for this meal? How much insulin should I dose to cover the consumption of this quantity of carbohydrates? If I eat too much fat, how will that delay the absorption of the carbohydrates, and won't that require altering the timing of my insulin dose for this particular meal? What is my anticipated level of activity following the meal? What happened to my blood glucose level last time I ate this amount of food at this restaurant? Patients require guidance through this difficult physiologic maze of uncertainty. Given the appropriate tools, patients can be successful in achieving their glycemic targets. Treatment protocols must be individualized and frequently reassessed; self-management of acute as well as chronic disease must be stressed at each visit.

The longer a person has diabetes, the less likely it is that endogenous insulin derived from pancreatic β -cells will help minimize glycemic excursions and variability. Although use of basal insulin combined with oral agents may successfully treat up to 60% of patients with type 2 DM to the glycosylated hemoglobin (A1C) target of <7.0% recommended by the American Diabetes Association,¹⁰ individuals with a baseline A1C >9.0% will often require prandial insulin to achieve a similar goal. Diabetes is a disease that is constantly changing. Patients often have to make acute treatment decisions on an hourly basis. Physicians should make long-term treatment decisions based on best-practice strategies at least quarterly.

Evaluating Postprandial Hyperglycemia

As people age, their 2-hour postchallenge blood glucose levels typically increase, often independent of their fasting glucose levels. At diagnosis, 25% of patients with type 2 DM have near-normal fasting glucose levels (<110 mg/dL).¹¹ The incidence of isolated impaired glucose tolerance (blood glucose levels of 140–199 mg/dL) is ~3 times greater than that of isolated impaired fasting glucose (blood glucose levels of 100–126 mg/dL). Therefore, most patients with newly diagnosed type 2 DM have isolated postchallenge hyperglycemia.¹¹ In the past, clinicians relied on fasting glucose levels for diagnosis and treatment decisions regarding glycemic control. However, increasing evidence now suggests that elevated postprandial glucose levels are independent risk factors for cardiovascular morbidity and mortality.¹¹ Minimizing acute postprandial hyperglycemic excursions should

lower A1C levels, reduce glycemic variability, and improve long-term outcomes.

In healthy euglycemic individuals, 2-hour postprandial blood glucose levels are usually <120 mg/dL and seldom >140 mg/dL. Blood glucose levels begin to rise ~10 minutes after glucose challenge, peak at ~1 hour, and return to preprandial levels 2 to 3 hours after a meal.¹² Carbohydrate absorption continues for 5 to 6 hours after the challenge. This excursion of postprandial hyperglycemia is mediated by the first-phase insulin response, which is characterized by a large endogenous release of insulin within 10 minutes of nutrient intake. Patients with type 2 DM have an absent or blunted first-phase insulin response. The delayed second-phase insulin response is unable to match pancreatic β -cell insulin secretion to what is required to minimize the acute increase in postprandial glucose levels. High postprandial glucose excursions result in programmed death of the pancreatic β -cells as well as peripheral insulin resistance.¹³

Effects of Postprandial Hyperglycemia on Endothelial Cell Stability

Hyperglycemia, whether acute (postprandial) or chronic, has tissue-damaging effects on a subset of cell types such as capillary endothelial cells of the retina, mesangial cells in the renal glomerulus, and neurons in the peripheral nerves.¹⁴ Why are some cells prone to develop complications whereas others appear to be immune to the effects of similar exposure to chronic hyperglycemia? The answer lies in a cell's ability to assimilate the amount of glucose required as an energy source before transporting nonessential glucose out of the cell. Cells that are inefficient interstitial transporters of glucose undergo oxidative stress, which induces endothelial dysfunction, vascular inflammation, and activation of pathways that trigger microvascular complications.¹⁵ Oxidative stress describes a condition in which intracellular production of reactive oxygen species challenges the capacity of cellular antioxidant defense systems, potentially leading to cellular dysfunction or damage.

Vascular endothelial cells form physical and biologic barriers between the vessel wall and the circulating blood cells, with the endothelium playing an important role in the maintenance of vascular homeostasis. Central to this role is the endothelial production of nitric oxide (NO), which is synthesized by the constitutively expressed endothelial isoform of NO synthase. Vascular diseases, including hypertension, DM, and atherosclerosis, are characterized by impaired endothelium-derived NO bioactivity that may contribute to clinical cardiovascular events. Endothelial cells exposed to oxidative stress generate high levels of reactive oxygen species via their mitochondrial electron-transport chain.¹⁶ Susceptible cells will activate biochemical pathways likely to progress toward long-term microvascular and macrovascular complications unless metabolic stability is restored.

Activation of the protein kinase C and nuclear factor- κ B (NF- κ B) pathways will increase the risk of developing diabetic nephropathy and retinopathy.¹⁷ Patients in whom

Evidence now suggests that elevated postprandial glucose levels are independent risk factors for cardiovascular morbidity and mortality.

the hexosamine pathway has been activated will likely develop cardiomyopathy and vascular dysfunction.¹⁸ Diabetic peripheral neuropathy is induced via activation of the polyol pathway.¹⁴

Although triglyceride levels are consistently measured in fasting blood specimens, accumulating evidence indicates that postprandial triglycerides further increase oxidative stress.¹⁹ As an underrecognized contributing factor to endothelial dysfunction, atherosclerosis, and cardiovascular events, hypertriglyceridemia activates NF- κ B (the redox-sensitive transcription factor) which, in turn, increases expression of multiple vascular inflammatory genes.²⁰

Just as a town's department of public transportation is responsible for repairing potholes that plague city streets, the body has the capacity to form a cellular "patch" over a site of acute endothelial injury. Derived from bone marrow, endothelial progenitor cells (EPCs) are mobilized to the peripheral circulation in response to tissue ischemia through the release of growth factors and cytokines. The EPCs hone into the ischemic or damaged tissue and stimulate endothelial repair. In addition to traditional cardiovascular risk factors, oxidative stress has been associated with reductions in the number and function of circulating EPCs, whereas an expanded EPC pool decreases cardiovascular mortality.²¹

Oxidative stress may even be induced in individuals without DM. Using a hyperglycemic clamp technique, euglycemic subjects exposed to ambient glucose levels >200 mg/dL for just 2 hours were found to have increased levels of urinary F2 isoprostanes (markers of oxidative stress).²² Exposure to blood glucose levels >180 mg/dL for just 4 hours can cause endothelial cell dysfunction and vascular inflammation that persist for up to 7 days, even if the blood glucose levels are subsequently normalized.⁶ One can certainly understand the critical link between oxidative stress and cardiovascular mortality. Pharmacologic interventions that target postprandial glucose excursions also reduce oxidative stress²³⁻²⁵ and vascular inflammation²⁶ while they improve endothelial function²⁷ and myocardial perfusion.²⁸

The concept of endothelial dysfunction has become widely recognized because it is a functional parameter that can be measured in humans at risk for vascular disease and because it is believed to be a link between complex phenomena at the molecular level and vascular pathologies such as atherosclerosis. In general, the action of endothelium-derived vasodilators (eg, NO and prostacyclin) has been associated with antiatherogenic mechanisms, whereas endothelium-derived vasoconstrictors (eg, endothelin-1 and thromboxane) have been associated with proatherosclerotic mechanisms.^{16,29}

NO is usually beneficial because it keeps the macromolecular barrier between the blood cells and the vascular wall (ie, the endothelial cells) smooth and free of adhesion molecules. NO also regulates vascular tone. However, peroxynitrite (an NO derivative) is formed when NO interacts with oxidative forces (superoxide) within endothelial cells. Peroxynitrite inhibits the endothelial cell's mitochondrial

electron transport system,³⁰ which leads to endothelial dysfunction and the transcription of endothelial-derived cytokines that induce pathways responsible for microvascular complications.³¹ Peroxynitrite also initiates lipid oxidation, which leads to atherosclerosis and macrovascular disease (Figure).³²

The production of peroxynitrite can be indirectly inferred by the presence of nitrotyrosine (NT) residues.³³ Increased NT has been found in the plasma of patients with DM, and evidence now suggests that acute postprandial hyperglycemia increases NT.³³

Experimental induction of hyperglycemia in normal subjects using a glucose clamp is sufficient to induce oxidative stress.²² Urinary F2 isoprostanes become elevated when euglycemic subjects are exposed to plasma glucose levels ranging from 200 to 250 mg/dL for just 2 hours. After completion of the hyperglycemic glucose infusion, urinary F2 isoprostane measurements normalize within 24 hours.

Monnier et al³⁴ suggested that deterioration of glucose homeostasis occurs in a 3-step process. Postprandial hyperglycemia becomes problematic once a patient's A1C level exceeds 6.5%. A1C levels ranging from 7.0% to 7.9% result in prebreakfast hyperglycemia followed by an "extended dawn phenomenon," or postmeal hyperglycemia, that may persist until the noontime meal. Chronic hyperglycemia, which is associated with nocturnal glucose elevations as well as postabsorptive hyperglycemia, occurs in patients with A1C levels >8.0%. Early and aggressive management of type 2 DM with the goal of achieving normal glycemia may slow the progression toward postprandial hyperglycemia and exposure to oxidative stress. The cytologic effects and the resulting complications of uncontrolled postprandial hyperglycemia are summarized in Table II.^{21,23,26,27,35-43}

Is the A1C Level the Only Predictor of Long-Term Risk in Patients with Diabetes Mellitus?

The recent decision by the National Institutes of Health to prematurely terminate one treatment arm of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study⁴⁴ suggests that the A1C is not the only tool for predicting long-term risks of DM. In this trial of adults with type 2 DM, the medical strategy for patients at especially high risk for heart attack and stroke (ie, to intensively decrease blood glucose levels to below current recommendations) was associated with a higher risk of death than was a less-intensive standard treatment strategy. Half of the participants in the intensive-treatment group achieved an A1C of <6.4%, whereas half of the participants in the standard-treatment group achieved an A1C of <7.5%. The ACCORD study enrolled 10,251 participants. Of these, 257 in the intensive-treatment group died, compared with 203 in the standard-treatment group. This is a difference of 54 deaths, or 3 per 1000 participants each year, over an average of almost 4 years of treatment. Even though extensive analyses by ACCORD researchers have not determined a specific cause for the increased deaths among the intensive-treatment group,⁴⁴ it

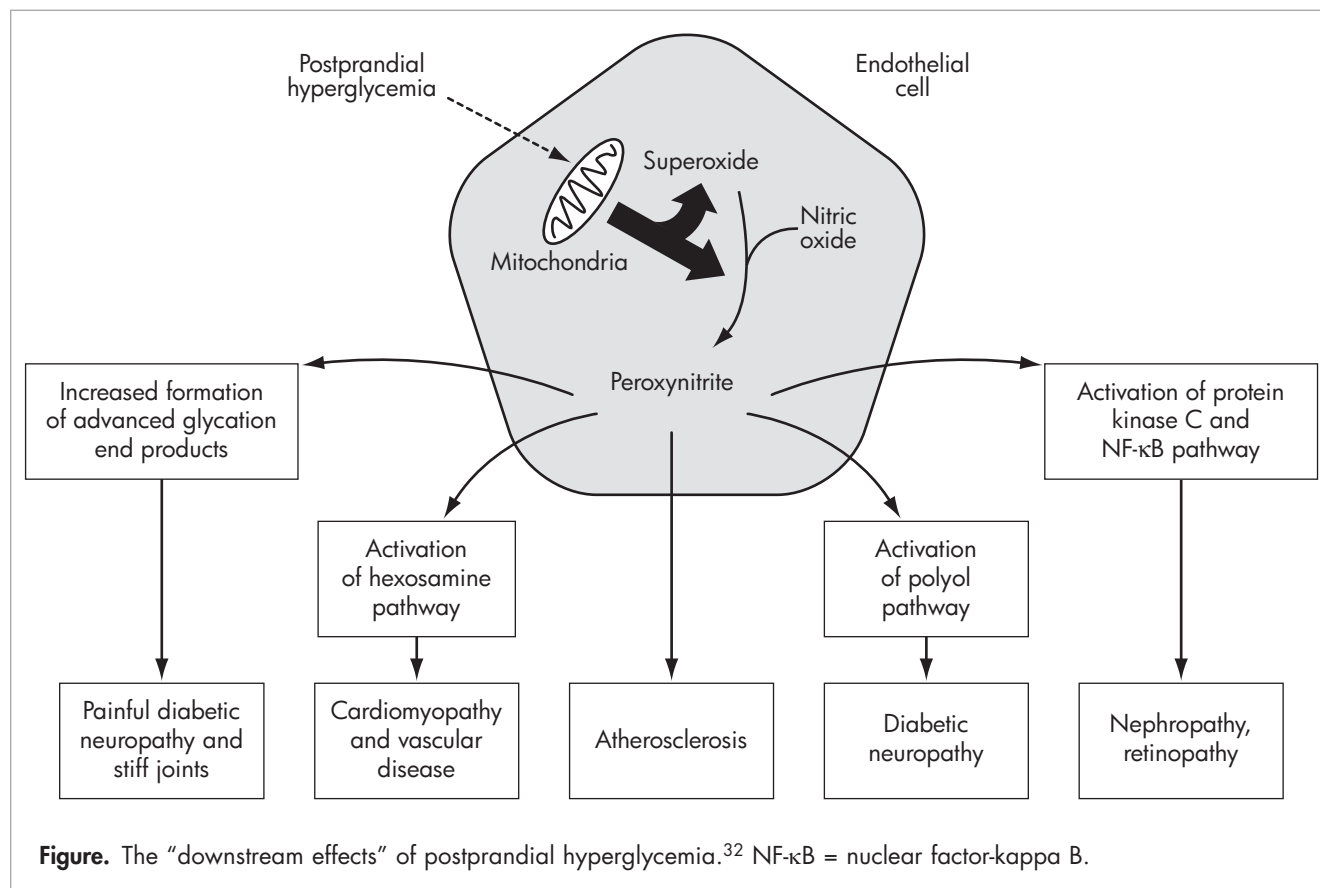


Figure. The “downstream effects” of postprandial hyperglycemia.³² NF-κB = nuclear factor-kappa B.

Table II. Suspected cause-and-effect relationship between uncontrolled postprandial hyperglycemia and long-term complications of diabetes mellitus.

Cytotoxicity Associated with Postprandial Hyperglycemia	Complication	References
Increased carotid intima-media thickness	Stroke	26
Vascular inflammation and atherosclerosis	Peripheral vascular disease, stroke, angina, coronary artery disease	35
Prothrombosis	Peripheral vascular disease, stroke, angina, coronary artery disease	36,37
Reduced levels of the cardioprotective cytokine interleukin-10	Unstable angina, neurogenic inflammation resulting in chronic pain	38,39
Elevated levels of the inflammatory cytokine, high-sensitivity C-reactive protein	Coronary artery disease, chronic pain	39,40
Endothelial cell dysfunction due to oxidative stress	Peripheral vascular disease, stroke, angina, coronary artery disease	23,27, 40-42
Hypertriglyceridemia	Peripheral vascular disease, stroke, angina, coronary artery disease	43
Reduction in circulating endothelial progenitor cells	Reduction in angiogenesis and vascular repair	21

would seem prudent to manage patients with DM using intensified lifestyle interventions and pharmacotherapy before patients develop microvascular and macrovascular complications.

The Diabetes Complications and Control Trial (DCCT) revolutionized diabetes care by confirming the association between hyperglycemia and late complications of diabetes.⁴⁵ The A1C constituted the primary parameter in the study by providing an integrated and reproducible measure of long-term glycemic control. Although attaining the lowest and safest A1C remains the standard benchmark by which successful therapy is determined,⁴⁶ other subtle aspects of glycemic control that are not predicted with an A1C should be evaluated in all patients.

In the DCCT, a cohort of patients from both the intensive- and conventional-treatment groups maintained an A1C of 9.0% throughout the study. Despite having identical A1Cs, the conventionally treated patients had a 50% higher risk of progression toward retinopathy than did the intensively treated patients. This increased risk of retinopathy is speculated to have been the result of wider daily glycemic variability in the conventionally treated cohort that could not be controlled with twice-daily insulin injections.⁴⁷ Patients undergoing multiple daily injections, although still exposed to chronic hyperglycemia, had less frequent and less significant postprandial elevations in glucose excursions and less oxidative stress than the conventionally treated patients.¹⁶

Based on this and other emerging evidence,⁴⁸ both glycemic variability (as a surrogate indicator of oxidative stress) and A1C (as a mathematical estimation of exposure to chronic hyperglycemia) should be considered as contributors to the risk for long-term complications of DM. Oxidative stress is an acute process associated with postprandial hyperglycemia and glycemic variability. Monnier et al⁴⁸ demonstrated that glucose fluctuations during postprandial periods, especially in patients with type 2 DM, elicited more oxidative stress than did chronic, sustained hyperglycemia.

Therefore, therapeutic interventions should be directed toward minimizing acute postprandial hyperglycemia, reducing glycemic variability, and treating patients to achieve the lowest and safest A1C targets. The treatment targets recommended by the American Diabetes Association are shown in **Table III**.⁴⁹

Treatment Modalities for Postprandial Hyperglycemia

Methods by which postprandial hyperglycemia and oxidative stress can be minimized are presented in **Table IV**.^{7,25,41,50-53} Three rapid-acting insulin analogues are designed to mimic the body's physiologic insulin response to meals. Research has shown that rapid-acting insulin analogues can reduce arterial oxidative stress and improve endothelial dysfunction.²⁷ Insulin lispro and aspart provide improved control of postprandial hyperglycemia and can be used within 10 to 15 minutes after meals, unlike regular human insulin, which must be injected 30 to 60 minutes before meals.⁵⁴ Glulisine is approved for injection up to 20 minutes after completion of a meal.⁵⁵

Table III. Targets for glycemic control as recommended by the American Diabetes Association Clinical Practice Guidelines.⁴⁹

Parameter	Recommended Target
A1C	<7.0%*
Preprandial plasma glucose	90–130 mg/dL
Postprandial glucose	<180 mg/dL†

A1C = glycosylated hemoglobin.

*The A1C goal for an individual patient is an A1C as close to normal (<6.0%) as possible without significant hypoglycemia. The A1C goal for patients in general is <7.0%.

†One- to two-hour peak postprandial capillary plasma glucose.

Table IV. Therapeutic approaches that can reduce postprandial hyperglycemia and oxidative stress.

Use insulin analogues preferentially over regular human insulin because their pharmacokinetic profiles mimic physiologic pharmacokinetic profiles more closely.^{7,50,51}

Advise patients to inject insulin 10 to 15 minutes before meals to allow the absorption of the insulin to match up more precisely with the onset of carbohydrate absorption from the gut.⁷

Consider using adjunctive therapy with pramlintide, which has been shown to improve many of the biochemical parameters of oxidative stress (weight loss, high-density lipoprotein cholesterol, blood pressure, glycemic variability, and triglycerides).²⁵

Instruct patients to reduce carbohydrate intake during meals to lose weight and reduce oxidative stress markers.^{41,52}

Encourage patients to exercise. Patients with type 2 diabetes mellitus have peripheral insulin resistance in skeletal muscle. Moderate aerobic exercising, 30 minutes daily, 5 days per week, within 1 hour of consuming the largest meal of the day, may help reduce postprandial hyperglycemia.⁵¹

Consider using exenatide twice daily to reduce the patient's weight and to improve markers of oxidative stress as well as cardiovascular risk.⁵³

To determine whether insulin therapy given to patients with type 2 DM could minimize markers of oxidative stress during the postprandial phase, Ceriello et al²⁷ studied 23 subjects with controlled type 2 DM (A1C levels $7.3\% \pm 0.5\%$) and 10 age-matched controls. None of the subjects smoked or had a history of lipid abnormalities or vascular disease. The patients received regular human insulin intravenously to maintain premeal (fasting) glucose levels between 130 and 150 mg/dL for 30 minutes. Before consuming a 600-kcal meal (50% carbohydrate, 30% fat, 20% protein), half of the patients with diabetes received an injection of regular insulin (0.15 unit/kg) 30 minutes before eating; the other half received an injection of insulin aspart (0.15 unit/kg) at the beginning of the meal. Control subjects received a single standard meal. NT, glucose, and triglyceride levels were evaluated immediately before and at 1, 2, 4, and 6 hours after each meal. Compared with regular insulin, insulin aspart demonstrated a statistically significant reduction in the area under the curve for postprandial hyperglycemia (58.3 ± 17.6 mg/dL vs 68.1 ± 17.7 mg/dL; $P < 0.04$), whereas no difference in triglyceride levels was observed between the 2 groups. NT, glucose, and triglyceride levels did not show any significant change during the postprandial phase in the normal subjects. This suggests that by quickly blunting the rise in postprandial hyperglycemia, rapid-acting insulin analogues (eg, aspart) can minimize the harmful effects of oxidative stress.

Exenatide, the first of a new class of medications known as incretin mimetics, enhances glucose-dependent insulin secretion, suppresses inappropriately elevated postprandial glucagon secretion, slows gastric emptying, and reduces food intake. Exenatide has also been shown to restore the acute responsiveness of pancreatic β -cells to secrete insulin.⁵⁶ This agent may be administered within 60 minutes of starting a meal. Patients receiving 10 μ g of exenatide twice daily for 82 weeks (30 weeks in the placebo-controlled trials and 52 weeks in open-label extension studies) had sustained reductions in A1C levels (-1.1%) and progressive reductions in body weight (-4.4 kg) relative to baseline with an adverse-event profile similar to that seen in the placebo-controlled trials.⁵³ Further analysis of the 82-week cohort revealed statistically significant changes from baseline for diastolic blood pressure (-2.7 mm Hg; 95% CI, -3.8 to -1.7), high-density lipoprotein cholesterol ($+4.6$ mg/dL; 95% CI, 3.7 to 5.4), and triglycerides (-39 mg/dL; 95% CI, -55.5 to -21.6).⁵³ A1C, weight, blood pressure, and lipids are all surrogate markers of oxidative stress.

Pramlintide, a synthetic analogue of human amylin, is administered as adjunctive mealtime endogenous therapy (ie, immediately before a major meal) for patients using insulin therapy. Pramlintide has been shown to reduce postprandial glucose excursions as well as other markers of oxidative stress such as total radical-trapping antioxidant parameter.²⁵

CONCLUSIONS

Patients with DM are at risk for developing microvascular and macrovascular complications. The likelihood of mini-

mizing that risk is based on the ability to avoid both acute hyperglycemia (which results in endothelial dysfunction due to oxidative stress, primarily during the postprandial state) and chronic hyperglycemia (which can be measured by monitoring A1C levels). Self-monitoring of blood glucose levels is useful in determining whether patients require more intensive postprandial glycemic control. Various pharmacologic interventions have been demonstrated to control both acute and chronic hyperglycemia, and physicians should consider methods to reduce acute oxidative stress, such as instructing patients in ways to achieve postprandial glucose levels <180 mg/dL. Fasting glucose levels should also be lowered to <110 mg/dL to decrease exposure to chronic hyperglycemia.

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Address correspondence to: Jeff Unger, MD, Unger Primary Care Medical Center & Catalina Research Institute, 12598 Central Avenue, Suite 219, Chino, CA 91710. E-mail: jungerm@aol.com