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

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Abstract

PURPOSE: Oxidative stress is the major mechanism thought to cause the microvascular and macrovascular complications commonly associated with type 2 diabetes. This paper will examine the evidence linking oxidative stress with long-term complications and discuss methods for minimizing its effect.

METHODS*:* A PubMed search of the literature was performed to identify the studies discussed in this review.

RESULTS*:* Although chronic hyperglycemia can be effectively monitored and targeted using A1C concentrations, postprandial glucose levels are also very important. Postprandial glucose excursions are exhibited by almost all patients with type 2 diabetes 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. Pharmacological interventions, such as rapid-acting insulin analogs that target postprandial glucose excursions, reduce oxidative stress, reduce vascular inflammation, and improve endothelial dysfunction.

CONCLUSIONS*:* Given the important role of oxidative stress in the development of complications associated with type 2 diabetes, it is important that physicians consider

methods to reduce oxidative stress that may occur during both acute (postprandial) and chronic hyperglycemia. One critical aspect of this will be 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 healthcare colleagues will minimize the risk of long-term complications associated with type 2 diabetes.

INTRODUCTION

The effects of chronic hyperglycemia, hyperlipidemia, and hypertension in patients with diabetes mellitus places these individuals at high risk for developing microvascular and macrovascular complications. Approximately 80% of patients with type 2 diabetes mellitus (T2DM) will succumb to cardiovascular complications such as stroke, peripheral arterial disease, and heart disease.[1] Although diabetes carries a 1.5- to 4.5-fold risk of cardiovascular mortality,[2] the microvascular complications patients experience (eg, retinopathy, nephropathy, and neuropathy) can have devastating effects on 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. Post-infarction mortality is significantly higher in the presence of acute hyperglycemia compared with infarcts occurring when glucose levels are physiologic.[3] Stroke patients presenting to the emergency department with glucose levels >160 mg/dL suffer greater neurological sequelae and have a greater mortality rate than stroke victims who are euglycemic.[4,5]

The causal mechanisms of microvascular and macrovascular complications are believed to be due to a process known as *oxidative stress*. Intracellular oxidative stress occurs when the production of reactive oxygen species (which are by-products 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 post-absorptive hyperglycemic excursions, health care providers can coach patients into maintaining "physiologic glycemia" and minimize long-term complications.

PATIENTS NEED PRACTICAL TOOLS TO BECOME SUCCESSFUL AT DIABETES MANAGEMENT

Although easier preached than accomplished, physicians must understand that, when provided with the appropriate tools, the majority of patients will become successful at diabetes self-management. Before labeling a patient with diabetes as being "non-compliant," 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 the insulin properly?

Prior to injecting, and in order to maintain physiologic postabsorptive glycemic control, the insulin user would have to know all of the information in Table 1.

TABLE 1. Physiologic Regulation of Postprandial Hyperglycemia for Patients With Diabetes

Regulating Factor	Comment	Reference
Timing of injection	• Rapid-acting insulin analogs and inhaled insulin should be dosed 10-15 minutes prior to eating. (Glulisine may be dosed up to 20 minutes following a meal) • Exenatide may be administered within 60 minutes of starting a meal • Pramlintide should be injected immediately prior to a major meal (≥ 250kcal or containing ≥ 30 g of carbohydrate)	Unger J. 2007.[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 meal and insulin dosing is important. "What happened last time I gave this amount of insulin for this type of meal under similar circumstances?"	Schmaderer J, Unger J. 2006.[9]
Dose Correction	• Time and amount of previous insulin bolus. If given within 4 hours, the current dose may need to be reduced by at least 20% to avoid insulin stacking and hypoglycemia • Timing of anticipated exercise. If exercise is planned within 2 hours of eating, meal time bolus will need to be reduced by 50%	Unger J. 2007.[7]
Rate of gastric emptying	• If gastric emptying is delayed and a rapid-acting insulin is given as usual (10-15 minutes prior to eating) the patient will experience a miss match between rapid insulin absorption and pharmacologic action with a delayed rise 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 2-3 hours after the injection is given.	Unger J. 2007.[7]
Counter-regulatory hormones	• *Hepatic glucose production* (HPG) is minimized by endogenous basal insulin secretion at the rate of 1 unit per hour. Insulin resistance and beta-cell death increases HPG, which	Unger J. 2007.[8]

	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 the pancreatic alpha cells in response to impending hypoglycemia. Glucagon causes the liver stores of glycogen to be converted 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.	

Clinicians should consider the mindset of the patient and understand that these individuals do NOT have a functioning pancreas. They are doing their absolute best to balance their glycemic excursions. They are using their brains to function as their pancreas. These patients require guidance through this very 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 and acute, as well as chronic, disease self-management must be stressed at each visit.

The longer a person has diabetes, the less likely it is that endogenous insulin derived from pancreatic beta cells will play a role in minimizing glycemic excursions and variability. Although basal insulin combined with oral agents may successfully treat up to 60% of patients with T2DM to the ADA-recommended glycosylated hemoglobin (A1C) target of

< 7%,[10] individuals with baseline A1C > 9% will often require prandial insulin to achieve a similar goal. Diabetes represents a disease that is constantly changing. It is not uncommon for patients to have to make acute treatment decisions on an hourly basis. Physicians should make long-term decisions on best practice management 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 T2DM have near-normal fasting glucose levels of < 110 mg/dL.[11] The incidence of isolated impaired glucose tolerance (blood glucose levels ranging from 140-199 mg/dL) is approximately 3 times greater than isolated impaired fasting glucose (blood glucose levels ranging from 100-126 mg/dL). Therefore, most patients with newly diagnosed T2DM have isolated postchallenge hyperglycemia.[11] Although clinicians have relied on the fasting glucose levels for both diagnosing and targeting ideal glycemic control in the past, increasing evidence now suggests that elevated postprandial glucose levels are independent risk factors for cardiovascular morbidity and mortality.[11] Minimizing acute hyperglycemic excursions during the postprandial periods should lower A1C, 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 postchallenge and peak at ~1 hour before returning to preprandial levels 2 to 3 hours

postmeal.[12] Carbohydrate absorption continues for 5 to 6 hours postchallenge. 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 T2DM have an absent or blunted first-phase insulin response. The delayed second-phase insulin response is unable to match pancreatic beta-cell insulin secretion to what is required to minimize the acute rise in postprandial glucose levels. High postprandial glucose excursions result in programmed death of the pancreatic beta cells as well as peripheral insulin resistance.[13]

EFFECTS OF POSTPRANDIAL HYPERGLYCEMIA ON ENDOTHELIAL CELL STABILITY

The harmful effects of acute (postprandial) and chronic hyperglycemia result in tissue damage to a subset of cell types such as capillary endothelial cells of the retina, mesangial cells in the renal glomerulus, and peripheral neurons.[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 any non-essential 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 triggering 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 both a physical and biological barrier between the vessel wall and the circulating blood cells. When endothelial cells are exposed to acute or chronic hyperglycemia they generate high levels of reactive oxygen species via their mitochondrial electron-transport chain.[16] The resulting oxidative stress is exacerbated in patients with hypertension, hyperlipidemia, and insulin resistance. 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 (PKC) and NF-kB pathways will increase the risk of developing diabetic nephropathy and retinopathy.[17] Patients in whom the hexosamine pathway has been activated will likely develop cardiomyopathy and vascular dysfunction.[18] Diabetic peripheral neuropathy is induced with activation of the polyol pathway.[14]

Just as a town's department of public transportation is responsible for repairing pot holes 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 compensatory angiogenesis. Oxidative stress—as well as all traditional cardiovascular risk factors—have been associated with a reduction in circulating EPCs, whereas an expanded EPC pool decreases cardiovascular mortality.[19]

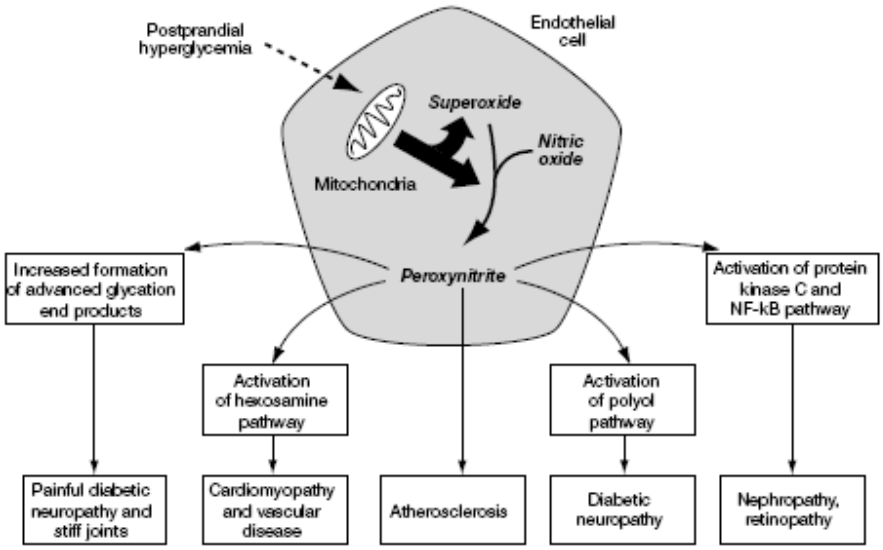
Oxidative stress may even be induced in individuals without diabetes. Using a hyperglycemic clamp technique, euglycemic subjects exposed to ambient glucose levels > 200 mg/dL for just 2 hours were found to have increased levels of urinary F2 isoprostanes, which is a marker of oxidative stress.[20] Exposure 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 stress[21-23] and vascular inflammation[24] while improving endothelial function[25] and myocardial profusion.[26]

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, example nitric oxide and prostacyclin) has been associated with antiatherogenic mechanisms, whereas endothelium-derived vasoconstrictors (eg, endothelin 1 and thromboxane) have been associated with proatherosclerotic mechanisms.[16,27]

Nitric oxide is most often 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. Nitric oxide also regulates vascular tone. However, a nitric oxide

derivative (peroxynitrite) is formed when nitric oxide interacts with oxidative forces (superoxide) within endothelial cells. Peroxynitrite inhibits the endothelial cell's mitochondrial electron transport system,[28] which leads to endothelial dysfunction and the transcription of endothelial-derived cytokines that induce pathways responsible for microvascular complications.[29] Peroxynitrite also initiates lipid oxidation, which leads to atherosclerosis and macrovascular disease (Figure 1).[30]

FIGURE 1. The "downstream effects" induced by postprandial hyperglycemia.



The production of peroxynitrite can be indirectly inferred by the presence of nitrotyrosine (NT) residues.[31] Increased NT has been found in the plasma of diabetic patients, and there is evidence that acute postprandial hyperglycemia induces an increase of NT.[31]

Experimental induction of hyperglycemia in normal subjects using a glucose clamp is sufficient to induce oxidative stress.[20] Urinary F2 isoprostanes (a byproduct of oxidative stress) become elevated when euglycemic subjects are exposed to plasma glucose levels ranging from 200-250 mg/dL for just 120 minutes. The urinary F2 isoprostanes measurements normalize within 24 hours of eliminating the hyperglycemic glucose infusion.

Monnier et al have suggested that the deterioration of glucose homeostasis occurs in a 3-step process.[32] Postprandial hyperglycemia becomes problematic once a patient's A1C exceeds 6.5%. A1C levels ranging from 7-7.9% result in pre-breakfast hyperglycemia followed by an "extended dawn phenomena," or post-meal 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%. Early and aggressive management of type 2 diabetes with the goal of achieving normal glycemia may slow the progression toward developing postprandial hyperglycemia and exposure to oxidative stress. The cytologic effects and the resulting complications of uncontrolled postprandial hyperglycemia are summarized in Table 2.

TABLE 2. Suspected Cause-and-Effect Relationship Between Uncontrolled Postprandial Hyperglycemia and Long-Term Diabetes Complications

Cytotoxity Associated With Postprandial Hyperglycemia	**Complication**	**Reference**
Increased carotid intima-media thickness (CIMT)	Stroke	Esposito K, et al. 2004.[24]

Vascular inflammation and atherosclerosis	Peripheral vascular disease, stroke, angina, coronary artery disease	Giugliano D, et al. 1997.[33]
Prothrombosis	Peripheral vascular disease, stroke, angina, coronary artery disease	Marfella R, et al. 2000.[34] Esposito K, et al. 2002.[35]
Reduced levels of the cardioprotective cytokine intraleukin-10	Unstable angina, neurogenic inflammation resulting in chronic pain	Smith DA, et al. 2001.[36] Unger J. 2007.[37]
Elevated levels of the inflammatory cytokine, high-sensitivity C-reactive protein	Coronary artery disease, chronic pain	Unger J. 2007.[37] Heitzer T, et al. 2001.[38]
Endothelial cell dysfunction due to oxidative stress	Peripheral vascular disease, stroke, angina, coronary artery disease	Ceriello A, et al. 2002.[21] Ceriello A, et al. 2004.[25] Heitzer T, et al. 2001.[38] Nappo F, et al. 2002.[39] West IC. 2000.[40]
Hypertriglyceridemia	Peripheral vascular disease, stroke, angina, coronary artery disease	Teno S, et al. 2000.[41]
Reduction in circulating endothelial progenitor cells	Reduction in angiogenesis and vascular repair	Fadini GP, et al. 2007.[19]

IS THE A1C THE ONLY PREDICTOR OF LONG-TERM RISK IN PATIENTS WITH DIABETES?

The Diabetes Complications and Control Trial (DCCT) revolutionized diabetes care by confirming the association between hyperglycemia and late-diabetic complications.[42] The A1C constituted the primary parameter in the study by providing an integrated and reproducible measure of long-term glycemic control in the studied patients. Although attaining the lowest and safest A1C remains the standard benchmark by which successful therapy is determined,[43] 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 conventionally treated groups maintained an A1C of 9% throughout the duration of the study. Despite having identical A1Cs, the conventionally treated patients had a 50% increased risk of progression toward retinopathy compared with the intensively managed patients. The reason for 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.[44] Patients taking 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,[45] both glycemic variability (as an surrogate indicator of oxidative stress) and A1C (as a mathematical estimation of exposure to chronic hyperglycemia) should be considered as contributors to risk for long-term complications. Oxidative stress is an acute process associated with postprandial hyperglycemia and glycemic variability. Monnier et al demonstrated that glucose fluctuations during postprandial periods, especially in patients with T2DM, elicited more oxidative stress than did chronic sustained hyperglycemia.[45] 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 American Diabetes Association recommended treatment targets are shown in Table 3.

TABLE 3. Targets for Glycemic Control as Recommended by the American Diabetes Association Clinical Practice Guidelines[46]

Parameter	**Recommended Target**
A1C	< 7%*
Preprandial plasma glucose	90-130 mg/dL
Postprandial glucose	< 180 mg/dL†

*The A1C goal for the 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.

TREATMENT MODALITIES FOR POSTPRANDIAL HYPERGLYCEMIA

Table 4 suggests methods by which postprandial hyperglycemia and oxidative stress can be minimized.

TABLE 4. Therapeutic Approaches That Can Reduce Postprandial Hyperglycemia and Oxidative Stress.

- Insulin analogs should be used preferentially over human regular insulin because their pharmacokinetic profiles are more similar to physiologic pharmacokinetic profiles[7,47,48]
- Advise patients to inject insulin 10 to 15 minutes prior to eating 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, HDL-C, blood pressure, glycemic variability, and triglycerides)[23]
- Reducing the carbohydrate intake for meals will result in weight reduction and the reduction of oxidative stress markers[39,49]
- Encourage patients to exercise. Patients with T2DM have peripheral insulin resistance at the site of the skeletal muscle. Initiation of moderate aerobic exercising, 30 minutes daily, 5 day per week, within 1 hour of consuming the largest meal of the day may help reduce postprandial hyperglycemia[48]
- Exenatide given twice daily can result in weight reduction and improve markers of oxidative stress and cardiovascular risk[50]

Three rapid-acting insulin analogs 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.[25] Insulin lispro and aspart provide improved control of postprandial hyperglycemia and can be used within 10 to 20 minutes of eating, unlike regular human insulin that must be injected 30 to 60 minutes prior to meals.[51] Glulisine is approved for injection up to 20 minutes following the completion of a meal.[52]

To determine if insulin therapy given to patients with T2DM could minimize markers of oxidative stress during the postprandial phase, Cereillo studied 23 subjects with satisfactory controlled T2DM (A1C levels 7.3 % $\pm$ 0.5)[25] None of the subjects smoked or had a history of lipid abnormalities or vascular disease. The patients were administered

regular human insulin intravenously to maintain a premeal (fasting) glucose levels between 130 mg/dL and 150 mg/dL for 30 minutes. Before consuming a 600 kcal meal (50% carbohydrate, 30% fat, 20% protein), half of the patients an injection of regular insulin (0.15 units/kg) 30 minutes prior to eating. The other half of the patients received an injection of insulin aspart (0.15 units/kg) at the beginning of the meal. Nitrotyrosine, glucose, and triglyceride levels were evaluated at 0 minutes, and at 1, 2, 4 and 6 hours after each meal . Compared with regular human insulin, insulin aspart administration significantly reduced the area under the curve of both glycemia and NT, whereas there was no difference in the reduction of triglyceride levels between the 2 groups. NT, glycemic, 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 insulins, such as aspart, can minimize the harmful effects of oxidative stress.

SUMMARY

Patients with diabetes are at risk for developing microvascular and macrovascular complications. The likelihood of minimizing risk is based upon 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–blood-glucose monitoring is useful in determining if patients require more intensive postprandial glycemic control.[53] Various pharmacologic interventions have been demonstrated to control both chronic and acute hyperglycemia, and physicians should consider ways to reduce acute oxidative stress,

such as instructing patients in ways to achieve postprandial glucose levels of <180 mg/dL. Fasting glucose levels should also be lowered to <110 mg/dL to lower the exposure to chronic hyperglycemia.

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