Chronic Hyperglycemia and Glucose Toxicity: Pathology and Clinical Sequelae

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Abstract: Type 2 diabetes mellitus (DM) is a progressive disease characterized by elevated plasma glucose levels. Type 2 DM results from a combination of factors affecting both peripheral tissue insulin sensitivity and β-cell function. A survey of the scientific literature on DM, glucose toxicity, hyperglycemia, nephropathy, neuropathy, reactive oxygen species, and retinopathy cited on PubMed/Medline from January 1975 to May 2011 was conducted. The relevant publications, chosen at the author's discretion, were used to synthesize this narrative review article. Chronic hyperglycemia imposes damage (glucose toxicity) on a number of cell types and is strongly correlated with the myriad of DM-related complications. Tissues most vulnerable to the effects of prolonged elevated plasma glucose levels include pancreatic β cells and vascular endothelial cells. The ensuing β-cell dysfunction promotes decreased insulin synthesis and secretion, further perpetuating the associated hyperglycemia. As for the vascular endothelium, chronic hyperglycemia is strongly correlated with many DM-related microvascular complications, including retinopathy, nephropathy, and neuropathy. The role of hyperglycemia in macrovascular complications is not well defined. Pathophysiologic modifications that arise in response to chronic hyperglycemia persist and may promote DM-related complications that manifest years later, even if plasma glucose levels have been brought under control. Increasing awareness of the mechanisms by which even modest hyperglycemia promotes long-lasting tissue damage highlights the need to achieve early tight glycemic control in patients with DM before substantial disease progression.

Keywords: β cell; glucose toxicity; hyperglycemia; microvascular complications; type 2 diabetes mellitus

Introduction

The American Diabetes Association (ADA) estimates that 25 million people in the United States have diabetes mellitus (DM), 90% to 95% of whom have type 2 diabetes mellitus (T2DM).[1] Worldwide, the World Health Organization estimates that > 346 million have DM.[2] This poses enormous costs, approximating $174 billion in the United States alone in 2007, and these numbers are expected to increase, impacting not only individuals but entire health care systems.[1] A large part of the cost stems from DM-related complications that include, but are not limited to, retinopathy, nephropathy, neuropathy, and cardiovascular disease.

A progressive deterioration of pancreatic β cells is characteristic of T2DM.[3] The nature of this underlying β-cell defect has not been clearly defined, but is central to the development and progression of T2DM. Genetic factors play a key role in the predisposition to impaired β-cell function and DM, and may be precipitated by other factors, such as insulin resistance and hyperglycemia.[4] Early in the course of the disease, there is a compensatory increase in circulating insulin levels to cope with the increase in insulin demand posed by insulin resistance.[5] In susceptible

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individuals, this compensation fails and hyperglycemia develops.[6] This chronic hyperglycemia further advances pancreatic β-cell dysfunction and also leads to reduction in β-cell mass.[4,7]

Prolonged exposure to elevated plasma glucose levels leads to toxic effects in a variety of cell types (glucose toxicity). In humans, there is a strong relationship between chronic hyperglycemia and impaired function of vascular endothelium,[8] with particular damage observed in retinal capillary endothelial cells and mesangial cells in the renal glomerulus.[9] Diabetes mellitus (including type 1 diabetes mellitus [T1DM] and T2DM) is the leading cause of all new cases of blindness in adults and accounts for approximately 44% of all new cases of renal failure in the United States.[1] In addition, injury to the microvasculature of the small vessels that supply the nerves contributes to neuropathy, which develops in 60% to 70% of all patients with DM.[1]

Managing chronically elevated glucose levels is crucial to reduce the risk of DM-related complications. Several large-scale studies have shown that the risk of developing these adverse outcomes can be significantly reduced if tight glycemic control is maintained.[10] The goal of this article is to provide clinicians with an overview of the pathology of chronic hyperglycemia to support the need for tight glycemic control at the earliest possible stage. The review will focus on the vascular pathology associated with prolonged hyperglycemia and will discuss the implications on pancreatic β cells.

Glucose Levels

The ADA's criteria for the diagnosis of DM include fasting plasma glucose (FPG) level $\geq$ 126 mg/dL (7.0 mmol/L) or 2-hour plasma glucose level $\geq$ 200 mg/dL (11.1 mmol/L) following an oral glucose load of 75 g.[11] A glycated hemoglobin (HbA$_{1c}$) level $\geq$ 6.5% was recently added as a threshold for diagnosis; however, there is some controversy about whether HbA$_{1c}$ levels should be used for diagnostic purposes given that the correlation between this measurement and FPG and/or 2-hour plasma glucose may be poor in some individuals. In addition, corresponding HbA$_{1c}$ level for a given plasma glucose level may vary among ethnic groups.[11] However, the advantages of using HbA$_{1c}$ level for diagnosis are that measurements are very precise, there is low intra-individual variability, it is convenient, does not require fasted blood sampling, and is less affected by other factors, including stress or intercurrent illness.[11] Glycated hemoglobin level reflects blood glucose levels over a 2- to 3-month interval, and regular monitoring of HbA$_{1c}$ levels plays a critical role in managing patients with DM.[11]

In addition to the estimated 25 million people in the United States with DM, another 79 million are projected to have pre-diabetes.[1] Given this high prevalence, targeting blood glucose level reductions among this at-risk population would be of great consequence in reducing the progression to T2DM.[11] The current ADA diagnostic criteria for prediabetes are FPG level of 100 to 125 mg/dL (5.6–6.9 mmol/L), 2-hour plasma glucose level of 140 to 199 mg/dL (7.8–11.0 mmol/L), and HbA$_{1c}$ level of 5.7% to 6.4%.[11]

Glucose toxicity is a pathologic consequence of prolonged hyperglycemia. However, it is not known how severe the hyperglycemia must be and how long must it persist for toxic effects to appear. As a treatment goal, the ADA recommends keeping an HbA$_{1c}$ level < 7.0%,[11] compared with the more rigorous criterion set by the American Association of Clinical Endocrinologists, which recommends that an HbA$_{1c}$ level $\leq$ 6.5% be kept.[12]

Effects of Chronic Hyperglycemia

For hyperglycemia to induce cellular damage, plasma glucose must first be transported across the cell membrane via facilitative glucose transporters. In skeletal muscle and adipose tissue, the rate of this process is drastically increased in the presence of insulin; however, most cell types do not require insulin for glucose uptake. When faced with a hyperglycemic environment, the majority of cells decrease the rate of intracellular glucose transport in order to maintain a relatively constant intracellular glucose level. In contrast, certain cell types cannot effectively regulate this process and are more vulnerable to elevated plasma glucose levels.[9] These cell types include pancreatic β cells, neuronal cells, and vascular endothelial cells, which equilibrate their intracellular glucose level to that of their extracellular environment.[3,9,13] Consequently, these tissues are highly susceptible to hyperglycemic damage as excess glucose enters the cell.

Mechanisms of Glucose-Induced Toxicity

The damaging effects of elevated intracellular glucose levels may stem from alterations in a number of pathways (Figure 1). These alterations include increased metabolism of glucose, resulting in the generation of superoxide radicals; a decrease in capacity of a key antioxidant enzyme, glutathione reductase; activation of protein kinase C (PKC); and irreversible glycation of proteins, resulting in formation of advanced glycation end-products (AGEs). Oxidative stress plays a central role in all of these, generally representing an imbalance between production and elimination of reactive oxygen species (ROS).[9]

Figure 1. Glucose toxicity occurs through 5 main mechanisms that begin when hyperglycemia leads to an increase in the intracellular glucose level. **A**) Increased glucose oxidation promotes the generation of superoxide. **B**) Production of sorbitol from excess glucose is increased, depleting NADPH and thereby limiting production of the antioxidant glutathione. **C**) Some of the excess glucose converted to fructose-6 phosphate enters the hexosamine pathway, whose products can affect gene expression, with adverse clinical consequences; excessive activity in the main energy pathway (the TCA cycle) also promotes ROS formation. **D**) Activation of the PKC system likewise results in the expression of factors that promote ROS formation and have detrimental effects on vessels and circulation. **E**) Glycation, or direct binding of glucose to proteins, produces structural changes that constitute an enduring cellular "memory" of the effects of hyperglycemia.
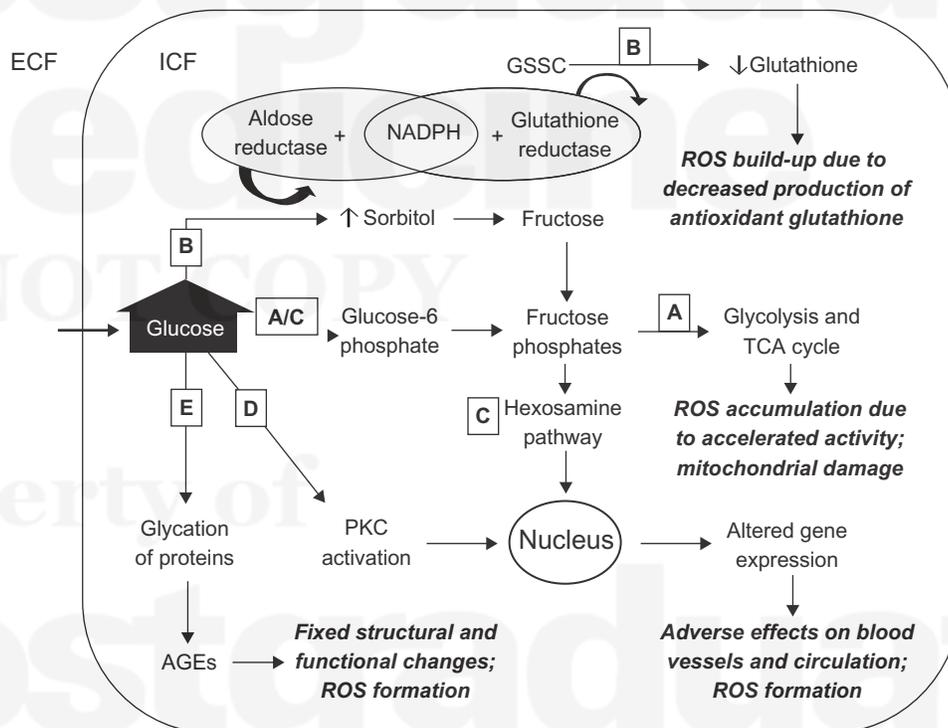
Abbreviations: AGE, advanced glycation end-product; ECF, extracellular fluid; GSSC, oxidized glutathione (which is reduced to the antioxidant form); ICF, intracellular fluid; NADPH, nicotinamide adenine dinucleotide phosphate (a key reducing agent in metabolic processes); PKC, protein kinase C (an intracellular signaling and regulatory system); ROS, reactive oxygen species; TCA, tricarboxylic acid (the TCA cycle is the main aerobic pathway).

Upon entry into the cell, glucose is metabolized and generates electron donors for transfer to the mitochondria, where they are used to make energy in the form of adenosine triphosphate. If more glucose is being oxidized, more electron donors are generated. However, when the mitochondrial capacity is exceeded, excess electron donors may form superoxide, an ROS (Figure 1, path A).[12]

An important antioxidant in the cell is glutathione (Figure 1, path B). Glutathione reductase, the enzyme that converts glutathione to its reduced form, which is critical for its antioxidant activity, requires the cofactor nicotinamide adenine dinucleotide phosphate (NADPH). NADPH becomes depleted when intracellular glucose levels increase excessively due to increased flux of glucose through the NADPH-dependent polyol pathway. When NADPH is depleted, generation of reduced glutathione is limited, leaving the cell vulnerable to the effects of ROS.[9,14]

Another mechanism by which elevated intracellular glucose levels promote the generation of ROS is via an increase in hexosamine pathway flux (Figure 1, path C). This involves metabolism of glucose to uridine diphosphate N-acetyl glucosamine, a glucose derivative that is incorporated into proteins, including transcription factors. As a result, expression of certain genes, such as plasminogen activator inhibitor-1, whose increased activity is associated with thrombosis, may be altered.[9]

Elevated intracellular glucose can also lead to the activation of the PKC pathway (Figure 1, path D). Protein kinase C signaling can promote expression of endothelial nitric oxide synthase and inhibit expression of endothelin-1, actions which collectively support vasodilation of blood vessels. Protein kinase C activity further signals a number of other proteins, which impact vascular function, permeability, angiogenesis, contractility, and coagulation.[9] Increased glucose drives the formation of diacylglycerol, the key cofactor required for activation of PKC. Of note, as tissues become progressively insulin resistant, insulin's promotion of increased endothelial nitric oxide synthase activity is diminished.[15] This pathway

is eventually lost, further reducing nitric oxide, while also increasing formation of the vasoconstrictor endothelin-1.[16]

Finally, chronic hyperglycemia drives glycation of intracellular proteins (Figure 1, path E).[14] These AGE precursors, which are elevated in patients with DM, can attack other proteins, inducing the formation of AGEs.[17,18] Advanced glycation end-products can inhibit mitochondrial respiration and increase the formation of intracellular ROS and inflammatory cytokines, both of which alter vascular function. Advanced glycation end-products are also potentially linked to the so-called "metabolic memory" phenomenon, whereby the toxic effects of glucose continue to impact a cell even after the offending chronic hyperglycemia is removed.

Pancreatic β Cells

Given the challenges of studying human β cells in vivo, much of the knowledge about β-cell function has been obtained from experiments using animal models. Some of these studies have suggested that lowering of plasma glucose levels may decrease hyperglycemia-induced β-cell dysfunction. For example, partially pancreatectomized diabetic rats have severely impaired insulin secretory defects.[19] In this animal model, treatment with phlorizin, a competitive inhibitor of sodium-glucose co-transporter 1 and 2, normalized plasma glucose levels via decreased reabsorption of glucose from the glomerular filtrate back into the circulation, and restored both first- and second-phase insulin secretion.[19] Moreover, increased glucose levels may contribute to excess generation of ROS, potentially through some of the mechanisms discussed previously (Figure 1), including enhanced PKC activity and elevated hexosamine pathway activation.[20] The oxidative stress that ensues mediates the deleterious effect that chronic hyperglycemia has on β-cell function.[4] Furthermore, islets, the small endocrine organs within the pancreas that are predominantly composed of β cells,[21] have the lowest antioxidant capacity of all metabolic tissues, decreasing their ability to restore reduction and oxidation (redox) balance.[22]

Postmortem isolation of islets from human donors with T2DM has enabled limited questions to be addressed. For example, glucose-stimulated insulin secretion is impaired in isolated islets from cadaver donors with T2DM, compared with those without T2DM.[23,24] This coincides with increased oxidative stress, as shown by elevated levels of various markers of oxidative stress.[23,24] Importantly, the addition of the antioxidant glutathione decreased the concentration of these stress markers and improved glucose-stimulated insulin secretion.[23] Increased expression of PKC was also detected in these isolated islets.[24]

In addition to insulin secretion, insulin gene expression is also dysregulated in the presence of chronic hyperglycemia.[7,23] Both islet volume density of insulin and its total pancreatic gene expression are reduced in pancreata from patients with T2DM.[23,24] Islets from patients with T2DM also have reduced numbers of mature insulin granules.[24] Furthermore, insulin is synthesized as a proinsulin precursor that undergoes processing within the insulin secretory granule. This cleavage is impaired in patients with T2DM, further illustrating the degree of β-cell dysfunction imposed by chronic hyperglycemia.[20]

Eventually, a critical decline in β-cell mass may occur on exposure to chronically elevated glucose levels. Pancreatic tissue samples from obese cadaver donors with either impaired fasting glucose or T2DM had reductions in β-cell mass of approximately 40% and 63%, respectively, relative to obese patients without T2DM.[25] This deficit is 41% in lean patients with T2DM. The most striking observation was the several-fold increase in β-cell apoptosis in the obese and lean patients with T2DM, compared with their counterparts without T2DM.[25] Data from diabetic animal models suggest that the increase in apoptosis is caused, in part, by exposure to high glucose levels.[26] Weir and Bonner-Weir[5] explain how "the concept of glucose toxicity is that β-cells normally function within a narrow range of plasma glucose levels and that even modestly higher glucose levels create an unnatural environment, which leads to alteration in function and most notably a loss of acute glucose-stimulated insulin secretion (GSIS)…we postulate that a loss of specialized gene expression leads to complete disruption of the acute phase of GSIS." All of these defects in β-cell function and mass lead to further reductions in insulin secretion, precipitating the substantial increases in plasma glucose levels seen in patients with T2DM.[5]

Despite the challenges of studying β-cell mass and function in humans in vivo, prospective studies have helped elucidate the course of β-cell dysfunction throughout the various stages of DM. Modeling of data from the Belfast Study, a 10-year prospective study that assessed β-cell function using homeostatic model assessment, suggests that patients who went on to develop T2DM already had a 40% to 50% reduction of β-cell function approximately 15 years before diagnosis.[27] These findings confirm that β-cell dysfunction occurs early in the progression of T2DM.

Micro- and Macrovascular Changes

The endothelium is the active inner monolayer of blood vessels forming a barrier between the circulating blood

and the vessel wall. It is vital in maintaining vascular homeostasis, which is required for adequate circulation and blood flow to tissues, and is an important factor in the pathogenesis of vascular disease in DM.[15,16] The endothelium maintains blood fluidity by regulating vascular tone and permeability, the balance between coagulation and fibrinolysis, inflammation, and cell proliferation.

Clinical Trials

Results from 2 large-scale trials have demonstrated that intensive glycemic control reduces the risk of developing DM-related complications. These have compared the effect of conventional versus intensive glucose-lowering therapy in patients with either T1DM or T2DM.[28,29] Intensive therapy consistently decreased the rate of development and progression of microvascular disease. In the Diabetes Control and Complications Trial (DCCT), 1441 young patients with T1DM were randomized to either intensive or conventional insulin therapy.[29] The mean HbA_{1c} levels after a mean of 6.5 years of treatment for patients with T1DM and T2DM were 7.4% and 9.1%, respectively. The adjusted mean risk of development of retinopathy, microalbuminuria, and neuropathy significantly decreased by 76%, 39%, and 60%, respectively, in the intensive glucose-lowering treatment group, compared with the conventional treatment group, with the rates of macrovascular-related events decreasing by 41%, although this finding was not statistically significant.[29]

Risk of microvascular complications was also significantly decreased in the UK Prospective Diabetes Study (UKPDS), in which 3867 patients with newly diagnosed T2DM were randomly assigned to either intensive treatment (insulin or sulfonylurea) or conventional treatment (diet and exercise) and followed for a mean of 10 years. Intensive treatment resulted in a 25% decrease in microvascular events ($P = 0.01$) and a 12% reduction in any DM-related endpoint ($P = 0.03$), accompanied by an 11% reduction in HbA_{1c} level (7.0% vs 7.9%).[28] However, there was no statistically significant improvement in macrovascular disease with intensive treatment.

The effects of chronic hyperglycemia on vascular-related complications are most intriguing in the corresponding observational follow-up studies to the DCCT and UKPDS. In the Epidemiology of Diabetes Interventions and Complications (EDIC) study, 93% of patients from the original DCCT were followed for an additional 11 years, during which no attempts were made to maintain participants at their original glycemic goals. Within 1

year, the difference in mean HbA_{1c} level between the 2 treatment groups narrowed (8% for the intensive vs 8.2% for the conventional treatment groups, respectively).[30] Despite similar hyperglycemia, over the course of the 11-year follow-up, participants initially assigned to the intensive treatment group sustained beneficial effects in DM-related outcomes, including lower rates and decreased progression of retinopathy and decreased progression of nephropathy.[31,32] Interestingly, they also had significant risk reductions in cardiovascular disease relative to the participants in the original conventional therapy group (42% decrease for any cardiovascular event; $P = 0.02$).[30] Of note, in patients who had T1DM for ≥ 30 years, the effects of intensive glucose lowering remained. The cumulative incidences of proliferative retinopathy, nephropathy, and cardiovascular disease were 21%, 9%, and 9%, respectively, in the intensive glucose-lowering treatment group, compared with 50%, 25%, and 14% in the conventional treatment group.[33] A 10-year follow-up to the UKPDS reported similar findings.[34] Despite the difference in HbA_{1c} level disappearing within the first year, 10 years later, any DM-related outcomes and microvascular disease were 9% and 24% lower, respectively, for participants originally in the intensive therapy group, compared with those in the conventional treatment group ($P = 0.04$ and $P = 0.001$, respectively). Additionally, occurrence of myocardial infarction decreased by 15% compared with the conventional therapy group ($P = 0.01$).[34]

These findings strongly indicate that intensive glucose-lowering therapy decreases the rates of both micro- and macrovascular complications over time. The effects of intensive treatment are sustained over many years, even after HbA_{1c} levels increase. This supports the notion that the early glycemic environment is "remembered" in target organs years later, a phenomenon referred to as metabolic memory. Although there were adverse events associated with the intensive glucose-lowering treatment (eg, hypoglycemia and weight gain) using the therapies available at the time, these were offset by the harmful and persistent effects of higher plasma glucose levels seen in the conventional treatment group.

Of note, in 3 other prospective studies in which patients with T2DM were randomized to intensive compared with conventional glucose-lowering therapy, the benefits of intensified glycemic control on T2DM complications were not as evident. In the Veterans Affairs Diabetes Trial (VADT), patients with long-standing T2DM (N = 1791) were randomized to receive either intensive or conventional

treatment (glimepiride and rosiglitazone or metformin plus rosiglitazone; insulin was added for patients who were not achieving the target HbA$_{1c}$ levels of < 6% and < 9% in the intensive and conventional treatment groups, respectively).[35] At 5.6 years, the mean HbA$_{1c}$ levels were 6.9% and 8.4% in the 2 groups, respectively; however, there were no statistically significant differences in the occurrence of micro- or macrovascular events between the groups. Similarly, in the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, patients with T2DM and preexisting cardiovascular disease (N = 11 140) were randomized to intensive or conventional treatment groups and followed for 5 years, during which mean HbA$_{1c}$ levels were 6.5% and 7.3%, respectively (addition of gliclazide to current therapy with sequential addition of insulin or other oral antidiabetic drugs vs current therapy; target HbA$_{1c}$ level ≤ 6.5% vs attainment of recommendations set by local guidelines for each group, respectively).[36] There was a small but statistically significant difference in major microvascular events (9.4% vs 10.9% for patients in the intensive treatment group vs those in the conventional treatment group), which was mostly a result of a difference in the incidence of nephropathy, although there were no statistically significant differences in retinopathy or macrovascular events.[36]

Lastly, in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients with T2DM and either cardiovascular disease or cardiovascular risk factors (N = 10 251) were examined.[37] The target HbA$_{1c}$ level in the intensive therapy group was < 6%, compared with 7% to 7.9% in the conventional treatment group (therapeutic regimens were individualized at the discretion of the investigator or patient based on response to therapy and assigned study group). After 1 year, the median HbA$_{1c}$ levels were 6.4% and 7.5% in the intensive and conventional glucose-lowering treatment groups, respectively; however, the intensive treatment arm was discontinued early due to an increase in all-cause mortality.

For clinicians, the findings from the VADT, ADVANCE, and ACCORD trials should not be viewed as discouraging, for several reasons. First, the studies included patients with long-standing T2DM; therefore, much of the toxic effects of glucose may have already occurred before intervention, and thus, the strategy of intensive glucose lowering may not be as effective in such patients. Second, even in the conventional treatment groups, HbA$_{1c}$ levels were still lower than those commonly seen in many patients with long-standing

T2DM; therefore, the rates of macrovascular events may have already been decreased in both groups, making the difference between them smaller. Third, patients in these latter trials were intensively treated for cardiovascular risk factors other than DM (eg, dyslipidemia and hypertension) compared with patients in the earlier DCCT/EDIC and UKPDS trials, again resulting in lower cardiovascular event rates, even in the conventional treatment group. Treatment of these additional cardiovascular risk factors is now standard care, but was not at the time of the UKPDS.

In light of the impact that chronically elevated plasma glucose levels have on the vascular endothelium and the increased incidence of retinopathy and nephropathy associated with DM, studies showed that biochemical markers of inflammation and ROS may serve as predictors of progression to either nephropathy or retinopathy in both T1DM and T2DM.[38] The data are less clear with regard to the effects of chronically elevated plasma glucose levels on macrovascular complications; however, long-term population and follow-up studies are beginning to unravel a potential connection between increased inflammatory markers and cardiovascular disease.[38] These findings highlight the need for therapies that will maintain plasma glucose at low enough levels to prevent or delay the effects of micro- and macrovascular damage.

Conclusion

As clinicians, we presently adhere to the following disease model for T2DM: Early in the disease course, insulin resistance induces a compensatory increase in pancreatic β-cell insulin secretion in an effort to overcome elevated plasma glucose levels caused by both reduced uptake of glucose into skeletal muscle and fat cells, as well as decreased suppression of glucose output by the liver. Over time, there is a progressive deterioration in β-cell function. Assuming no lifestyle and/or therapeutic interventions are adopted, this decline in β-cell function, in combination with insulin resistance, results in insufficiently low production and secretion of insulin, and a chronic hyperglycemic state predominates that will eventually reach the diagnostic criteria of T2DM.

Regardless of its pathophysiologic mechanism, DM is a lifelong disease with dire consequences for patients and health care systems. Although glycemic control is only part of the comprehensive management of DM, chronic hyperglycemia should be recognized as a direct source of diabetic pathology rather than merely as a biochemical marker of inadequate disease control (Table 1). Chronic hyperglycemia imposes damaging effects on a number of tissues,

leading to the development of DM-related complications, including nephropathy, retinopathy, neuropathy, and cardiovascular disease. Importantly, these damaging effects persist even if plasma glucose levels have normalized. This metabolic memory can be explained in part based on the mechanisms by which prolonged hyperglycemia affects the cell. In addition to the toxic effects of glucose on the vasculature, pancreatic β cells are also highly susceptible to the damaging effects of chronic hyperglycemia.

Results from long-term studies in patients with DM underscore the importance of early tight control of plasma glucose levels. However, this approach can increase the risk of hypoglycemia and even weight gain with some currently available therapies. These findings highlight the need for a balanced approach with the focus on maintaining plasma glucose levels as close to normal as possible without exposing patients to excessive adverse events. Lifestyle and/or therapeutic interventions should be initiated early in the course of the disease to enhance the benefits of glucose lowering in light of the fact that tissues "remember" their former hyperglycemic environment, with resulting toxic effects persisting. Screening programs leading to early intervention may be useful in identifying individuals with undiagnosed T2DM who may be at high risk for developing DM-related complications.

Table 1. Key Concepts for Clinicians

- In the United States, ~25 million people have DM.[1]
- Chronic hyperglycemia further advances pancreatic β-cell dysfunction.[4,7]
- Prolonged exposure to elevated plasma glucose levels leads to toxic effects in a variety of cell types (glucose toxicity), including pancreatic β cells, neuronal cells, and vascular endothelial cells.[3,9,13]
- Early management of chronically elevated plasma glucose levels is crucial to reduce the risk of DM-related complications, including retinopathy, nephropathy, neuropathy, and cardiovascular disease.[28–34]
- The damaging effects of elevated intracellular glucose levels may stem from alterations in a number of pathways[9,12,14–18]:
  - Increased metabolism of glucose, resulting in the generation of superoxide radicals
  - A decrease in capacity of glutathione reductase (a key antioxidant enzyme)
  - Activation of PKC
  - Irreversible glycation of proteins, resulting in formation of AGEs
  - Oxidative stress and the formation of ROS
- Results from large-scale clinical trials demonstrate that intensive glucose-lowering therapy reduces the risk of DM-related complications.[28,29]
- Given the high prevalence of DM in the United States, early screening and resulting lifestyle and therapeutic interventions to reduce blood glucose levels may be of great benefit.

Abbreviations: AGE, advanced glycation end-product; DM, diabetes mellitus; PKC, protein kinase C; ROS, reactive oxygen species.

Conflict of Interest Statement
Carlos Campos, MD, MPH, CDE is a consultant/advisor for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, and Novo Nordisk, and serves on the speakers bureau for AstraZeneca, Bristol-Myers Squibb, and Novo Nordisk.

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