Glycemic Control and Complications in Type 2 Diabetes Mellitus

Mark Stolar, MD
Department of Clinical Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA

ABSTRACT

Current guidelines for treating patients with type 2 diabetes mellitus are based on glycemic standards derived from epidemiologic data; however, the course of the disease, from prediabetes to end-stage complications, is not the same in all patients. Microvascular complications, including nephropathy, retinopathy, and neuropathy, are strongly related to hemoglobin A1c (HbA1c). However, vascular complications may progress in patients who have HbA1c \(< 7.0\%\) and may appear even in undiagnosed patients owing to transient increases in plasma glucose concentrations. Concomitant atherosclerosis and occult macrovascular disease may follow an accelerated course in type 2 diabetes. Macrovascular complications may develop early, and, like microvascular complications, do not correlate linearly with HbA1c. Managing hyperglycemia in the later stages of type 2 diabetes does not appear to be associated with improved cardiovascular outcomes. The glucotoxicity and lipotoxicity that may precede prolonged hyperglycemia and \(\beta\)-cell dysfunction are early, reversible pathophysiologic events. This suggests that prompt management may modify the course of hyperglycemia and prevent or delay long-term complications. The challenge remains to identify patients with early type 2 diabetes who are at risk for rapid progression of \(\beta\)-cell decline and premature development of microvascular complications. Ongoing research into the mechanisms responsible for diabetic complications may provide new markers to help identify patients with type 2 diabetes who can benefit from earlier antidiabetes treatments.

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Most patients who have type 2 diabetes mellitus develop vascular complications despite a variety of available antidiabetes medications and improved methods of assessing disease progression. The current type 2 diabetes disease model supports more aggressive treatment later in the course of the disorder and less aggressive treatment in its earlier stages. However, there is a growing argument to invert this treatment paradigm and aggressively identify and treat type 2 diabetes earlier to reduce the morbidity and mortality associated with advanced disease. This review investigates the factors that limit the long-term success of current antidiabetes regimens, focusing on the complications associated with hyperglycemia and the concept of applying therapeutic thresholds to disease progression. The review also reinforces the concept that early and progressive loss of \(\beta\)-cell function and mass is a key component of type 2 diabetes pathophysiology, and that more aggressive \(\beta\)-cell conservation and timely glycemic control may mitigate the risk of vascular complications.

THE CURRENT STATE OF DIABETES CARE

Approximately 24 million persons in the United States have diabetes, of which type 2 diabetes accounts for the vast majority of cases. Based on the National Health and Nutrition Examination Survey (NHANES) 1999 to 2002 data, \(~73\) million Americans have diabetes or impaired fasting glucose (IFG), a condition that increases the risk for diabetes. A retrospective cohort study using the database of a healthcare maintenance organization, showed that nearly 25% of individuals with newly acquired abnormal fasting glucose (110 to 125 mg/dL [1 mg/dL = 0.05551 mmol/L]) go on to develop type 2 diabetes, most within 2.5 years.
Other cohorts have shown an even greater propensity for conversion to diabetes, but predictors for the rate of conversion for any given individual remain elusive. As many as 11% of individuals with impaired glucose tolerance (IGT) may already have early-stage microvascular disease. The American Diabetes Association (ADA) considers IFG (fasting plasma glucose of 100 to 125 mg/dL) and IGT (2-hour plasma glucose of 140 to 199 mg/dL) as categories of prediabetes.

The present goal of type 2 diabetes therapy is to reduce hemoglobin A1c (HbA1c) to <7% or ≤6.5%, according to guidelines set forth by the ADA and the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE), respectively. Although many patients with type 2 diabetes are aware of HbA1c goals and are receiving therapy to lower their HbA1c, data from NHANES indicate that greater improvement in glycemic control is possible. NHANES data for 1999 to 2000 showed glycemic control rates (defined as the proportion of patients with HbA1c <7%) of 35.8% for patients with type 2 diabetes. In NHANES 2003 to 2004, ~57% of patients diagnosed with diabetes achieved the HbA1c goal of <7%. Thus, despite the abundance of available antidiabetes therapies, a considerable number of patients with type 2 diabetes continue to have relatively poor glycemic control and are at risk for macrovascular and microvascular disease.

Current guidelines specify evidence-based target HbA1c goals for patients with diabetes, including type 2 diabetes. However, various factors, such as age, ethnicity, and co-morbidities contribute to different expression of disease patterns in patients with similar degrees of glycemic control. For instance, there is a gradual decrease in years of life lost by patients as they age, ranging from a mean of 25.9 years in patients diagnosed with diabetes before 35 years of age, to 0.9 and 1.6 years in patients diagnosed at and beyond 85 years of age, respectively. This indicates that duration, as well as the severity of abnormal glycemia, affects patient outcomes. As anticipated, about 50% of the mortality in these patients resulted from cardiovascular disease (CVD).

Along with CVD, HbA1c has been shown to be an independent predictor of healthcare costs in adult patients with diabetes. In a prospective analysis (N = 1,694 adults with diabetes) of data from a patient survey and medical claims over a 3-year period, elevated HbA1c predicted higher healthcare costs in those who had baseline HbA1c >7.5% (P = 0.015). In this study, pharmacoeconomic benefits were seen in groups of patients whose HbA1c declined from 10% to 9%, from 9% to 8%, and from 8% to 7%, with associated mean overall healthcare cost differentials over 3 years of US$1,374 (P < 0.05), $1,303 (P < 0.05), and $373 (P = NS), respectively. This study supports glycemic control data from earlier studies showing that aggressive management of HbA1c reduces the risk of microvascular complications in patients with type 1 diabetes and type 2 diabetes.

### Glycemic Control and Microvascular Complications

The incidence and prevalence of neuropathy, retinopathy, and nephropathy increase with the duration of diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) 35 demonstrated that HbA1c is strongly related to microvascular effects in patients with type 2 diabetes. Over a mean follow-up of 10 years, which was equivalent to the duration of type 2 diabetes in the study, a 1% reduction in HbA1c was associated with a 37% reduction in microvascular complications and a 43% reduction in amputation or death from peripheral vascular disease. During the same period, a reduction in the incidence of macrovascular complications, including stroke, myocardial infarction (MI), heart failure, and cataracts, was not as pronounced, ranging from 12% to 19%.

The UKPDS findings expand on the data from the Diabetes Control and Complications Trial (DCCT), which showed a hyperbolic risk progression for microvascular complications as HbA1c values increased in patients with type 1 diabetes. Patients in the intensive therapy group achieved a median HbA1c of 7.2%, compared with 9.1% in the conventional therapy group over a mean follow-up of 6.5 years. Intensive therapy reduced the adjusted mean risk for retinopathy 76% (95% confidence interval [CI], 62% to 85%) in the primary prevention cohort and reduced the occurrence of microalbuminuria 39% (95% CI, 21% to 52%) and of clinical neuropathy 60% (95% CI, 38% to 74%) in the combined primary and secondary intervention cohorts. In addition, UKPDS 35 showed the adjusted rate of microvascular events was ~14% in patients with type 2 diabetes who had HbA1c between 7% and 8% at study end.

HbA1c is an easily measured indicator of hyperglycemia, but other measures of end-organ dysfunction and microvascular complications may better reflect risk and the need for treatment in individual patients, particularly when HbA1c is between 7.0% and 8.0%. Research into mechanisms associated with hyperglycemic tissue damage such as production of superoxides or advanced glycation products may eventually lead to clinical tests capable of identifying patients at high risk of diabetic complications.

Hyperglycemia induces tissue damage through mitochondrial superoxide production. Cells damaged by hyperglycemia include capillary endothelial cells in the retina, mesangial cells in the renal glomerulus, and neurons and Schwann cells in peripheral nerves. These cells are at particularly high risk for damage because they are unable to regulate uptake of glucose during hyperglycemia.

Increased intracellular glucose drives the production of reactive oxygen species (ROS) through the induction of electron buildup in the mitochondrial electron transport...
chain. These ROS damage nuclear DNA, which triggers repair by poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP). PARP modifies glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and other nuclear proteins by adding polymers of ADP-ribose to the proteins. This reduces GAPDH activity, which, in turn (1) activates the polyol pathway; (2) increases intracellular advanced glycation end-product (AGE) formation; (3) activates protein kinase C (PKC) and, subsequently, nuclear factor–κB; and (4) activates hexosamine pathway flux.

The polyol pathway is responsible for increasing susceptibility to intracellular oxidative stress and has been shown to affect nerve conduction velocity in diabetic animal studies. The production of AGEs leads to both microvascular and macrovascular disorders, including retinopathy, nephropathy, and accelerated atherosclerosis. Increased PKC affects the expression of a variety of genes and has been linked to early changes in the retinas and kidneys of patients with diabetes. Activated hexosamine pathway flux leads to pathologic gene expression linked to abnormalities of glomerular cell gene expression and cardiomyocyte dysfunction, increasing the potential risk of the understated glycemic complication of congestive heart failure (CHF).

Historically, it was believed that microvascular complications of diabetes, including type 2 diabetes, developed only after ~10 to 15 years of active disease. However, it is increasingly clear that complications may begin at lower glucose concentrations or during sporadic increases in glucose rather than after current thresholds for the diagnosis of type 2 diabetes are consistently reached. The prevalence of diabetic neuropathy increases significantly with the progression from normal glucose tolerance (NGT) to IFG, IGT, and type 2 diabetes. Accordingly, in the Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Research in the Region of Augsburg (MONICA/KORA) S2 and S3 surveys, 7.4%, 11.3%, 13%, and 28% of patients with NGT, IFG, IGT, and diabetes (92% had type 2 diabetes), respectively, were found to have polyneuropathy (overall P <0.001).

The same gradual increase in prevalence is observed with albuminuria. The prevalence of microalbuminuria (i.e., unadjusted for age and sex) detectable in patients with IFG and IGT is 8.3% and 9.9%, respectively, and increases to 15.4% in patients with new-onset diabetes, with the highest rates (~26.5%) observed in patients with long-standing type 2 diabetes. Because microvascular symptoms are detected before diagnostic criteria for type 2 diabetes are met, there is evidence against waiting for prediabetes to progress before initiating antidiabetes treatment in patients manifesting early signs of glycemic complications.

HbA1c is a function of postprandial and fasting hyperglycemia, which in turn have been associated with an increased incidence of microvascular disease. The effects of postprandial and fasting hyperglycemia on overall hyperglycemia change as HbA1c varies. When HbA1c is <7.3%, postprandial hyperglycemia contributes ~70% to the measured glycemia and fasting hyperglycemia contributes ~30%. As HbA1c increases, postprandial hyperglycemia contributes less and fasting hyperglycemia contributes more to the glycemic burden. When HbA1c reaches 8.5%, fasting hyperglycemia contributes ~55% and postprandial hyperglycemia contributes ~45% to the glycemic burden, this is changed to ~70% and ~30%, respectively where HbA1c reaches 10.2%. The precise impact of hyperglycemia (fasting or postprandial) on microvascular complications may differ, depending on factors such as age and baseline HbA1c. However, knowing the predominant type of hyperglycemia may have therapeutic implications, because certain pharmacotherapies have a greater effect on postprandial than fasting hyperglycemia.

Additional studies are needed to determine the extent to which microvascular disease correlates with adverse outcomes without the presence of comorbidities; for example, how often a patient with type 2 diabetes and trace microalbuminuria goes on to develop significant renal disease without concomitant hypertension or hypercholesterolemia. It is also not known whether patients remain at increased risk if their hypertension and hypercholesterolemia, which contribute to macrovascular disease, are treated aggressively but their hyperglycemia is not at goal.

**HYPERGlyEMIA AND MACROVASCULAR DISEASE**

Hyperglycemia, as measured by HbA1c, is a predictor of coronary heart disease (CHD) risk. In a Finnish study that followed elderly men and women (of whom ~16% and ~19% had type 2 diabetes, respectively, at baseline) for up to 3.5 years, HbA1c >7.9% were associated with a 21% incidence of CHD-related events and a 12% incidence of CHD mortality (P <0.05). In the Norfolk cohort of the European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk), 82% of the excess mortality associated with HbA1c ≥5% was accounted for by the 70% of the population whose HbA1c was between 5% and 6.9%. It is not clear from these findings at which HbA1c percentage the transition from disease risk to accelerated event causation occurs.

The relation between glucose tolerance and the development of CVD has been investigated in several studies. The Paris Prospective Study showed a 2-fold increase in CHD mortality in patients with IGT and a 2.5-fold increase in patients with known diabetes. The Finnish study showed elevated fasting and postprandial insulin concentrations to be strongly predictive of the development of coronary disease at 5 years, independent of other risk factors, including glucose concentrations. A meta-regression analysis of several longitudinal studies suggests a linear relation between both fasting and prandial glucose and CVD, with such risk extending into the nondiabetes range. This risk is somewhat stronger for prandial than for fasting glucose (relative risk, 1.58 [95% CI, 1.19 to 2.10] vs. 1.33 [95% CI, 1.06 to 1.67]).
Data from the Nurses’ Health Study showed that many individuals are at increased CV risk before their diagnosis of type 2 diabetes is made. In this analysis, the women who entered and remained nondiabetic throughout the study were assigned a baseline risk of 1. For women diagnosed with type 2 diabetes during the trial, there was a 2.82-fold increase in relative CV risk before their diagnosis and a 3.71-fold increased risk after their diagnosis. Women who had been diagnosed with type 2 diabetes before study entry had a 5-fold increased risk of CV events. This might argue not for tighter glycemic control in prediabetes as much as for maintaining normoglycemia.36

Early development of macrovascular complications during the course of hyperglycemic disease was also evident in a study of 164 patients admitted to the coronary care units of 2 hospitals with a first MI but no previous diagnosis of diabetes. Glucose tolerance tests showed that 35% of these patients had IGT and 31% had diabetes at discharge. In a recent study, the relation between glucose normalization and clinical outcomes was evaluated in 7,820 patients hospitalized with acute MI (~50% with diabetes). Patients also had elevated blood glucose concentrations on admission (≥140 mg/dL). Odds ratios (95% CI) for mortality were 2.1 (1.3 to 3.5) and 13.0 (8.0 to 21.3), respectively, for patients with mean postadmission glucose of 110 to <140 mg/dL and ≥200 mg/dL, respectively, versus <110 mg/dL, suggesting that lower mean postadmission glucose was associated with better survival rates. No statistically significant differences in mortality rates were observed between insulin-treated and noninsulin-treated patients across the range of glucose concentrations following admission. These data suggest a significant impact of hyperglycemia and insulin-resistance on the development of CVD.36,37

Risk of CV events also appears to be higher in earlier-onset type 2 diabetes (occurring before 38 years of age) than in later-onset type 2 diabetes (occurring before 60 years of age). In a 3-year observational study, the risk of developing macrovascular disease was twice as high in younger adults with early-onset type 2 diabetes as in their older counterparts (hazard ratio [HR], 7.9 vs. 3.8). This difference was seen over a relatively short observation period, suggesting that factors beyond simple glycemia may be involved, and it is attractive to speculate greater inflammation/atherogenesis may be linked to accelerated β-cell dysfunction. Other factors, such as increased body mass index, elevated diastolic blood pressure, and lower high-density lipoprotein cholesterol, may be seen in earlier-onset type 2 diabetes.39

The mechanisms surrounding glycemic control and CVD may help to explain elevated CV risk in patients with prediabetes. CV events and the development of atherosclerotic plaques are ultimately driven by LDL in the setting of subendothelial inflammation. Although hyperglycemia may not greatly affect LDL or the inflammatory response, it does have an impact on platelet aggregability and development of AGEs, which are associated with changes in the subendothelial matrix and accelerate oxidative stress and LDL oxidation.40 These glucose-driven mechanisms typically are more closely associated with atherogenesis than with event causation. Conversely, oxidative stress may be more strongly linked to CV event causality, as well as atherogenesis, and may be activated by acute glucose fluctuations. Continuous glucose monitoring has been used to compare the effects of sustained chronic hyperglycemia and acute glucose fluctuations on the urinary excretion of 8-iso prostaglandin F₂α, a marker of oxidative stress. As glycemic excursions increase, so does oxidative stress.41 This may partially explain the epidemiologic association between impaired postprandial hyperglycemia (i.e., IGT) and CV event risk, which is not seen with IFG.

The development of atherosclerosis in type 2 diabetes may represent an accelerated process from nondiabetic atherosclerosis that warrants differential or aggressive treatment and preventive measures. In 1 pathologic study, 36 lipid-rich atheromas from patients with diabetes were compared with 32 atheromas from nondiabetic individuals (Figure 1).42 Inflammation, neovascularization, intraplaque hemorrhage, and reparative collagen (type III) were quantified and found to be significantly different based on diabetes status. The diabetic atheromas were associated with greater inflammation, neovascularization, and reparative collagen than were the NGT atheromas (P <0.001).42 These results suggest that increased inflammation and neovascularization are associated with an increased reparative process involving collagen type III that may contribute to plaque progression unique to diabetes.40,42

Despite mechanistic differences, standard treatment of patients with hyperglycemia has been shown to reduce the incidence of CV events. A meta-analysis involving 14 diabetes studies (including 8 in type 1 diabetes, involving 1,800 patients, and 6 in type 2 diabetes, involving 4,472 patients) demonstrated that improved glycemic control, achieved through a reduction of HbA₁c, reduced the incidence of macrovascular events in the evaluated trials for patients with diabetes.43 Moreover, in a study by Esposito and colleagues,44 the control of postprandial plasma glucose (PPG) was shown to lead to a regression of carotid atherosclerosis. A comparison of the effect of repaglinide and glyburide on carotid intima-media thickness (CIMT) changes in 175 treatment-naive patients with type 2 diabetes showed that regression of CIMT was associated with decreased markers of inflammation.44 It is unclear whether lower PPG levels or a more favorable postprandial lipid inflammation milieu is ultimately responsible.

Several large studies provide evidence regarding the impact of intensive glycemic control on CV complications, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,45 the Diabetes and Vascular Disease: Preterax and Diamicro Modified Release Controlled Evaluation (ADVANCE) study,46 and the Veterans Affairs Diabetes Trial (VADT).47 None of these studies found a significant benefit for aggressive glucose lowering on CV events, although there was a reduction in microvascular complications, primarily through a decrease in the risk.
of nephropathy. However, there is an inherent risk to using these studies to definitively determine the effects of aggressive treatment of hyperglycemia on CV risk. The patients in these studies had type 2 diabetes for 8 to 11 years, with more than a third also having a positive history of CVD as well as multiple CV risk factors. The challenge is that the additive benefits of intensive glucose control may be difficult to demonstrate in this patient population. The effects of glycemic lowering are also confounded because some patients were more aggressively and concomitantly treated for hypertension and hyperlipidemia.

One controversial finding in the ACCORD study associated intensive antidiabetes management with increased mortality. This finding was not supported by the ADVANCE trial. Notably, patients in the ACCORD study had known heart disease or additional CV risk factors at baseline, a mean baseline HbA1c of 8.3% and a 10-year duration of diabetes. Moreover, given the atherosclerotic profile of these patients, it is unclear whether the aggressive glycemic lowering actually may have led to greater plaque instability.

In the VADT, during a median 5.6-year follow-up, no significant difference was seen between the intensive- and standard-therapy groups in any component of the primary outcome, which was time to occurrence of a major CV event that was a composite of MI, stroke, CV death, CHF, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene (HR in the intensive-therapy group, 0.88; 95% CI, 0.74 to 1.05; \( P = 0.14 \)) or in all-cause mortality between the 2 groups (HR, 1.07; 95% CI, 0.81 to 1.42; \( P = 0.62 \)).

Post hoc analyses of these type 2 diabetes studies suggested that patients with a disease duration of <12 years may have benefited from intensive treatment. Moreover, in a subset of patients who underwent coronary or aortic computed tomography calcium scoring at baseline, a lower coronary artery calcium score at baseline was associated with better outcomes with intensive therapy than was a higher calcium burden at baseline.

Similarly, the UKPDS 80 study evaluated long-term glucose control on atherosclerotic risk factors or events such as microvascular complications and MI. This included surviving patients from the original UKPDS cohort who underwent post-trial monitoring for up to 10 years postintervention. Patients in the treatment phase, which included conventional therapy (i.e., diet) or intensive therapy (i.e., sulfonylurea, metformin, insulin), reduced microvascular
risk and emergent risk reductions for MI and death from any cause. This was sustained over 10 years of follow-up, but it is not clear whether it will be sustained further. However, if these observations are accurate and a legacy effect does exist, treatment guidelines may need to be inverted, as the goal would then become more aggressive treatment earlier in the course of the disease rather than later.

**DIABETES MELLITUS: ROLES OF GLUCOTOXICITY AND GLUCOLIPOTOXICITY**

Many clinicians believe that glucotoxicity plays a role in β-cell function, amplifies lipotoxicity, and reduces β-cell mass. Under current treatment models, glucotoxicity would not be considered a complication of type 2 diabetes because antidiabetes treatment is warranted only after a patient has reached a certain degree of β-cell dysfunction, as evidenced by fasting hyperglycemia. Just as microvascular and macrovascular complications begin before current treatment protocols prescribe intervention, β-cell dysfunction may begin before blood glucose levels increase. Once hyperglycemia occurs, it may cause additional defects in insulin secretion and insulin action. In fact, the progression of type 2 diabetes parallels the decline in β-cell function. In Figure 2, data from the UKPDS show about a 50% reduction of β-cell function at the time of diagnosis of type 2 diabetes.

Hyperglycemia also has been correlated with negative cellular responses in β-cells. Chronic hyperglycemia has been shown to cause β-cell hypertrophy and greatly increase the risk for apoptosis. Chronic exposure to hyperglycemia leads to the de-differentiation of β-cells and increased stress as measured by ROS and antioxidant gene production. Endogenous insulin secretion is improved after exogenous insulin therapy. However, once β-cell mass has declined sufficiently, it can be surmised that this improvement would no longer occur.

**SUMMARY**

Almost 50% of patients with type 2 diabetes have HbA1c above the generally recommended goal of <7%. However, microvascular complications may occur in many patients whose HbA1c is below the current target. A recent understanding of the biochemical pathology of microvascular complications may lead to development of novel disease markers and treatments to help identify and manage patients before they are diagnosed with type 2 diabetes.

Macrovascular complications may represent the greatest cause of morbidity in patients with type 2 diabetes. Recent large studies, such as ACCORD and VADT, suggest that
the late adoption of intensive glycemic treatment may be detrimental to CV outcomes. Underlying atherosclerosis develops early in the disease process, when intensive glycemic control appears to be most advantageous. There is compelling evidence to support that not all patients with type 2 diabetes benefit equally from current treatment guidelines that call for action at a standard HbA1c goal, and that improved markers for more rapid disease progression and complications are needed to more aggressively manage the subpopulation of patients with diabetes who are at greatest risk of microvascular and macrovascular complications.

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