Glycemic Exposure, Glycemic Control, and Metabolic Karma in Diabetic Complications

Merlin C. Thomas

Diabetes continues to cast a long shadow over the lives of many people. It is now clear that even transient hyper- or hypoglycemia or increased glycemic variability around healthy mean glucose levels can have long-lasting and long-term effects on the development and progression of diabetic complications, including cardiovascular disease, kidney disease, retinopathy, and neuropathy. Even after glycemic control has been achieved and maintained for many years, it appears hard to undo the changes that are instilled, including epigenetic programming, compositional changes, post-translational modifications, or simply lead time toward an inevitable fate. This phenomenon has become known as "metabolic memory" or the "legacy effect," but it may be better characterized as "metabolic karma," in which the intent and actions of an individual (with respect to metabolic control) influence the future health of that individual. This "bad karma" has been used to explain many clinical observations surrounding diabetes and its management, including the lack of benefits in many short- and intermediate-term trials, and the potential utility of early intensive glycemic control. Further understanding the molecular basis of a metabolic legacy in diabetes will certainly provide new targets for intervention.

Key Words: Diabetes, Diabetic nephropathy, Legacy, Memory, Epigenetics

Introduction

Healthy glycemic control is not merely the absence of chronic hyperglycemia. The functions of the pancreas serve not only to postprandially prevent hyperglycemic excursions but also to prevent interprandial hypoglycemia to maintain a continuous invariable glucose supply to the brain and other glucose-dependent tissues. If this system of checks and balances fails, then it has acute consequences. However, it is now clear that even transient hyper- or hypoglycemia or increased glycemic variability around healthy mean glucose levels can have long-lasting and long-term effects on the development and progression of diabetic complications, including cardiovascular disease,[1] kidney disease,[2] retinopathy,[3] and neuropathy.[4] This phenomenon has become known as "metabolic memory"[5] or the "legacy effect,"[1] but it may be better characterized as "metabolic karma," such that the intent and actions of an individual (with respect to metabolic control) influence the near and distant future of that individual. This phenomenon has been used to explain many clinical observations surrounding diabetes and its management, including the lack of benefits in many short- and intermediate-term trials.[6] More recently, metabolic karma has also been used to promote the concept of early intensive diabetes management as a means to establish a long-term legacy of good health. However, the physiological mechanism(s) responsible for metabolic karma are still poorly defined. This article will explore the paradigm of metabolic karma, the potential mechanisms contributing to it, and its implications for diabetes care.

Transient Hyperglycemia Is Enough to Cause Complications

In prediabetic states, the ability to correct for glucose loading is impaired because of the combined effects of insulin resistance and impaired glucose-stimulated insulin production, leading to transient (often postprandial) elevations in blood glucose even in the absence of chronic hyperglycemia or abnormal mean glucose control. However, even these small and transient elevations appear to be sufficient to initiate a range of pathogenic pathways and are associated with increased risk of albuminuria, cardiovascular disease, and other adverse outcomes, including premature mortality.[7,8] It is important to note that this risk is independent of whether or not these individuals ever develop overt diabetes. One reason may be the metabolic legacy of transient hyperglycemia.

It is certain that transient exposure to hyperglycemia has long-lasting in vivo physiological effects.[1,9-12] In experimental settings, it is possible to briefly expose animals to diabetes/hyperglycemia and observe the persistent effects on gene expression and complications. For example, studies performed in dogs with diabetes demonstrated that retinopathy was suppressed if glucose control was achieved within the first 2.5 years of hyperglycemia, but it progressed if glucose control was achieved after this time.[13] Likewise, we have shown that diabetic mice develop progressive atherosclerosis, even if diabetes is subsequently eliminated by treatment.[9]

From Baker IDI Heart & Diabetes Institute and Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia.

Financial Disclosure: The author declares that there are no relevant financial interests.

Address correspondence to Merlin C. Thomas, MBChB, PhD, Baker IDI Heart & Diabetes Institute, 75 Commercial Road, Melbourne, 3004, Australia. E-mail: merlin.thomas@bakeridi.edu.au

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.03.004

Transient Hypoglycemia

Although the acute effects of hypoglycemia are well known, the long-lasting changes induced by transient or recurrent hypoglycemia are less well described, but they may include autonomic dysfunction, neuronal damage, and hypertension.[14] Recurrent hypoglycemia is also associated with upregulation of proadhesion/proinflammatory pathways in the aorta of mice.[15] It is certain that hypoglycemia is an important risk factor for adverse outcomes in patients with diabetes, but whether it is a marker of suboptimal glycemic control or a direct mediator of adverse outcomes remains controversial. Some of these changes may be reversed by scrupulous avoidance of hypoglycemia, suggesting they are not subject to a prolonged metabolic legacy. However, detailed exploration of the many epigenetic effects of recurrent hypoglycemia, especially in the brain, is only now underway.

Glycemic Variability

Patients with the same mean hemoglobin A1c (HbA1c) can have markedly different glycemic control. Some individuals have increased variability around the mean, meaning an increased frequency of highs and lows. In so far as the amplitude of postprandial glycemic excursions or counter-regulatory hormonal responses to hypoglycemia may also influence complications, there is plausible grounds to suggest that glycemic variability might be related to microvascular complications in diabetes beyond simply mean control. However, in the Diabetes Control and Complications Trial (DCCT) trial, there was no evidence that variability in the HbA1c influenced the development of complications beyond the achieved HbA1c. By contrast, in the Renal Insufficiency And Cardiovascular Events (RIACE) study, HbA1c variability was independently correlated with albuminuria in patients with type 2 diabetes.[2] The accurate measurement of glucose variability unfortunately requires methods for analysis other than HbA1c, which does not capture any variability on a smaller scale of hours or days, which may influence the development or progression of complications. Such studies requiring more comprehensive or continuous glucose monitoring are now feasible and are currently underway. At least at this stage, analyses of type 1 and type 2 diabetic patients have suggested that only average glycemia (mean blood glucose and HbA1c), and not glycemic variability markers (eg, mean amplitude of glycemic excursion), is associated with adverse outcomes.[16] However, the effect of glycemic variability of microvascular and macrovascular outcomes may be strikingly different, as was observed in the RIACE study.[2]

CLINICAL SUMMARY

- Transient hyper- or hypoglycemia or increased glycemic variability around healthy mean glucose levels can have long-lasting and long-term effects on the development and progression of diabetic complications, including cardiovascular disease, kidney disease, retinopathy, and neuropathy.
- Metabolic karma or legacy may explain the lack of benefits in many short- and intermediate-term trials and the potential utility of early glycemic control.

The Legacy of Previous Glycemic Control

The concept of a legacy that arises out of periods of good or bad glycemic control is supported by follow-up findings of large clinical trials. In type 1 diabetes, the DCCT documented that patients who received intensive treatment during the DCCT period (7.3% vs 9.0%) benefited, with a slower incidence and progression of diabetic microvascular complications relative to those who were in the conventional treatment group. Long-term follow-up of this cohort in the Epidemiology of Diabetic Complications and Interventions study demonstrated a persistently reduced complications rate (for nephropathy, retinopathy, hypertension, and cardiovascular disease) in patients randomized to receive intensive treatment for over a decade after the original study, although the large differences in HbA1c between the 2 treatment groups that existed during the study had dissipated within a year of the completion of the DCCT.[17-22]

A similar phenomenon was observed in the United Kingdom Prospective Diabetes Study (UKPDS) post-trial study of patients with type 2 diabetes, in which macro- and microvascular protection afforded by intensive glycemic control strategies, achieving an average HbA1c of 7.0% over conventional treatment, averaging 7.9%, was persistent for at least a decade after differences in glycemic control between intensive and conventionally treated patients had disappeared at the end of the first year post-trial.[23,24] By contrast, the clear benefits afforded by intensive blood pressure control observed during the UKPDS did not persist once the differences in blood pressure between intensive and conventionally treated patients had also disappeared in the post-trial follow-up.[25] Such data imply that any legacy of hyperglycemia must be more than simply to advance complications.

The clinical significance of a glycemic legacy is potentially wide reaching. It suggests that efforts today to control glucose levels can have long-term gains whereas suboptimal management today may have effects for many years to come. Moreover, any "karma" is likely to be more evident if good glycemic control is attained early in the natural history of the disease rather than late (after