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Should minimal blood glucose variability become the gold standard of glycemic control?

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Abstract

The Diabetes Complications and Control Trial (DCCT) established glycosylated hemoglobin (A1C) as the gold standard of glycemic control, with levels ≤7% deemed appropriate for reducing the risk of vascular complications. Yet, even when A1Cs were comparable between intensively treated subjects and their conventionally treated counterparts, the latter group experienced a markedly higher risk of progression to retinopathy over time. Our speculative explanation, based on the discovery that hyperglycemia-induced oxidative stress is the chief underlying mechanism of glucose-mediated vascular damage, was that glycemic excursions were of greater frequency and magnitude among conventionally treated patients, who received fewer insulin injections. Subsequent studies correlating the magnitude of oxidative stress with fluctuating levels of glycemia support the hypothesis that glucose variability, considered in combination with A1C, may be a more reliable indicator of blood glucose control and the risk for long-term complications than mean A1C alone.

Keywords: Diabetes complications; Glucose variability; Oxidative stress; Reactive oxygen species

1. Introduction

The Diabetes Complications and Control Trial (DCCT) revolutionized diabetes care by confirming the association between hyperglycemia and late diabetic complications (DCCT Research Group, 1993). Glycosylated hemoglobin (A1C) constituted the primary parameter in the study because it provides an integrated measure of glycemic exposure. Considered the "gold standard" of glycemic control, A1C remains the preeminent benchmark of successful therapy, with levels ≤7% deemed appropriate for reducing the risk of vascular complications (American Diabetes Association, 2004). Yet, the possibility that more subtle aspects of glucose homeostasis, beyond those represented by A1C, could affect the development or progression of microvascular complications was raised by the DCCT investigators themselves. In a 1995 report evaluating the association of A1C levels before and during the DCCT with the risk of retinopathy progression in patients receiving either conventional or intensive therapy, the authors surmised that updated mean A1C is "not the most complete expression of the degree of glycemia" and that the risk of complications may be more highly dependent on other factors (DCCT Research Group, 1995). Their statement rested largely on the observation that the risks of retinopathy progression associated with a given level of mean A1C differed significantly between intensively and conventionally treated patients after 5 to 9 years ($P<.01$; Fig. 1). Participants in the intensive treatment group exhibited minimal change in the risk of progression to retinopathy over time, whereas their conventionally treated counterparts experienced a marked escalation of risk, despite comparable A1Cs.

Our speculative explanation for this phenomenon was that there was a greater frequency and magnitude of

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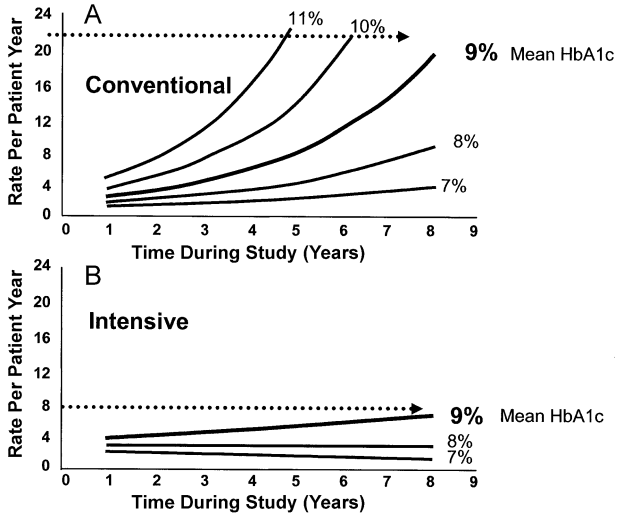

Fig. 1. Absolute risk of sustained retinopathy progression as a function of updated mean A1C (percentage) during the DCCT and the time of follow-up during the study (years), estimated from absolute (Poisson) regression models. (A) Conventional treatment group. (B) Intensive treatment group. Reprinted with permission from DCCT Research Group (1995); © American Diabetes Association.

glycemic excursions in conventionally treated patients, who received fewer insulin injections than did patients in the intensive group. We further postulated that an increased magnitude of glycemic variability would generate more reactive oxygen species (ROS) in complications-prone cells because hyperglycemia-induced oxidative stress, resulting from the overproduction of ROS by the mitochondrial electron-transport chain, is the chief underlying mechanism of glucose-mediated vascular damage (Brownlee, 2001). The ability to quantify oxidative stress in relation to glycemia has provided added insight into the ways in which acute increases in blood glucose, via the production of ROS, affect aspects of physiologic homeostasis. Based on this emerging evidence, we hypothesize that glucose variability, considered in combination with A1C, is a more reliable indicator of blood glucose control and the risk for long-term complications than mean A1C alone.

2. Evidence of the importance of glycemic variability

Although ROS cannot be measured directly, these unstable molecules interact with biological macromolecules such as proteins, lipids, and DNA, to generate numerous oxidative products (Betteridge, 2000). Of these, nitrotyrosine and 8-hydroxydeoxyguanosine (8-OHdG) have been evaluated to determine the extent of vascular damage induced by periodic versus continuous exposure to high glucose (Ceriello, Quagliaro, Catone, et al., 2002; Quagliaro et al., 2003). Examination of downstream targets of ROS, such as cell apoptosis (Risso, Mercuri, Quagliaro, Damante, & Ceriello, 2001), the activation of nuclear factor (NF)-κB in mononuclear cells (Schiekofer, Andrassy, Chen, et al., 2003), and cell growth and collagen synthesis in cultured human tubulointerstitial cells (Jones, Saunders, Qi, & Pollock, 1999), has also demonstrated the pathological effects of blood glucose variability.

Quagliaro et al. (2003) investigated the differential effect of variable glucose concentrations versus stable high glucose on high-glucose-induced ROS generation, measured by nitrotyrosine and 8-OHdG levels, and the effects of that oxidative stress on cellular apoptosis, amplifying previous data showing that apoptosis is markedly increased in human umbilical vein endothelial cells (HUVECs) exposed to periodic exaggerations of hyperglycemia (Risso et al., 2001). As predicted, cells cultured in an intermittent glucose condition simulating "real-life" glycemic fluctuations typical of patients with diabetes produced larger amounts of both nitrotyrosine and 8-OHdG compared with constant high and normal glucose conditions. Moreover, exposure of HUVECs to fluctuating glucose concentrations was found to induce a greater increase in the activity of protein kinase C (PKC), a known consequence of hyperglycemia-induced ROS formation, than did stable high glucose (Du, Matsumura, Edelstein, et al., 2003; Quagliaro et al., 2003).

In a study of patients with Type 2 diabetes and matched healthy control subjects, fasting nitrotyrosine was significantly increased in diabetic individuals and was further elevated after meals in these patients, but not in the nondiabetic controls (Ceriello et al., 2002). Because nitrotyrosine is a marker of the production of peroxynitrite, a highly reactive free radical derived from superoxide and nitric oxide, it is conceivable that the postprandial state, particularly in people with pronounced hyperglycemia, may have important pathogenic implications.

A comparison of the effects of constant versus alternating hyperglycemia on cultured human proximal tubular cells (PTCs) and cortical fibroblasts (CFs) with respect to cell growth, collagen synthesis, and cytokine secretion revealed enhanced responses following conditions of alternating blood glucose (Jones et al., 1999). Collagen synthesis as a measure of extracellular matrix production was unchanged in PTCs and CFs exposed to constant hyperglycemia, but the presence of intermittent high glucose yielded increases of 29% (±10%, $P<.05$) and 65% (±28%, $P<.01$) in PTCs and CFs, respectively. Secretion of the cytokine TGF-β1 increased more dramatically in PTCs exposed to alternating (352%) versus constant high glucose (230%); while in CFs, secretion of the cytokine IGFBP-3 was more greatly enhanced (intermittent, 216%; constant, 128%). The authors concluded that variability in glycemic control could be more deleterious to the cells of the tubulointerstitium than constant of high blood glucose, although constant levels of near-normal blood glucose would be least damaging of all.

Finally, diabetic retinal vessels and renal glomeruli contain increased levels of advanced glycation end-products (AGEs). It has been shown that the binding of AGEs, such as carboxymethyllysine (CML), to AGE receptors (RAGE)