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Controlling the complications of diabetes: It's about the sugar

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The debate over whether glucose control is a critical factor in preventing complications of type 2 diabetes mellitus is nearing its conclusion. For years, the role of so-called glucotoxicity has been challenged by theoretical arguments that the level of glycemic control might not sufficiently explain or allow prevention of complications of diabetes. Other factors, such as dyslipidemia, hypertension and cigarette smoking, are substantially responsible for these complications, and controlling these factors does reduce mortality significantly. However, mounting evidence, the most compelling of which is from a recent meta-analysis showing that intensive control of glucose prevents myocardial infarction,[1] points to glucose control as the remaining culprit. When we practitioners tolerate random glucose levels above 11 mmol/L or hemoglobin A_{1c} (HbA_{1c}) levels above 8% because they are "close enough," we are allowing unnecessary harm to patients.

The hypothesis of glucose toxicity states that hyperglycemia impairs both insulin secretion and sensitivity, shifting superfluous glucose from the normal glycolytic pathway to the minor sorbitol, hexosamine and glycation pathways. The accumulated end products of these pathways cause oxidative stress and inflammation in cells and blood vessel walls, resulting in pancreatic β-cell dysfunction and systemic atherosclerosis.[2] Observational studies involving people with type 2 diabetes mellitus have shown a clear association between glycemic control and micro- and macro-vascular outcomes.[3] However, the most pragmatic and convincing test of the glucose toxicity hypothesis comes from randomized trials of intensive glucose control.

The importance of tight control of glucose levels has been clearly established in type 1 diabetes, where there is an absolute deficiency of insulin. In the Diabetes Control and Complications Trial (DCCT) involving adults with type 1 diabetes, achieving an average HbA_{1c} of 7% with intensive glycemic control led to a 30%–76% reduction in the microvascular complications of retinopathy, nephropathy and neuropathy; longer follow-up showed a 57% reduction in coronary artery disease.[4] In type 2 diabetes, the UK Prospective Diabetes Study (UKPDS) found significant and sustained reductions in microvascular complications in patients who were given insulin and sulfonylurea to achieve an HbA_{1c} of 7%.[5] Recently, longer follow-up of the same study participants found that, despite a loss of the difference in HbA_{1c} levels after the trial, myocardial infarction was reduced by 15% among nonobese patients given sulfonylurea and insulin and by 33% among obese patients given metformin; all-cause mortality was also reduced in this group.[6] Similarly, the recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which achieved an average HbA_{1c} of 6.4% in the treatment arm versus 7.5% in the control arm, found a 24% reduction in the hazard of nonfatal myocardial infarction, albeit that this trial was stopped prematurely because of increased all-cause and overall cardiovascular mortality in the intensive glycemic control group.[7] These 2 trials give convincing support for the idea that hyperglycemia is at least an important cause of the excess burden of myocardial infarction in type 2 diabetes.

Residual doubt about the glucose toxicity hypothesis stems from problems with trial design, such as poor baseline risk stratification, small sample size, short treatment duration and poor delivery of the glucose control intervention. The new meta-analysis[1] pooled the UKPDS and ACCORD trials with 3 other ones that addressed these prior weakness. In total, 33 040 clinically stable nonhospitalized patients were enrolled and followed for about 5 years. The mean intervention HbA_{1c} level of 6.6% was 0.9% lower among those in the intensive treatment groups. They experienced a significant 17% reduction in incidence of nonfatal myocardial infarction and a 15% reduction in coronary events overall. No effect on all-cause mortality was found, a result encumbered by heterogeneity among trials. There was, as expected, a higher incidence of hypoglycemia and severe hypoglycemia in the intensive groups, particularly in the 3 trials that reached average HbA_{1c} levels below 7%, a caveat that cannot be ignored.

We know enough to end the debate over whether glycemic control matters — it does. While we must continue learning how best to achieve this safely, sufficient evidence permits agreement on a provisional optimum target: an HbA_{1c} level of 7% for every patient with type 2 diabetes, especially for those with new-onset diabetes and for younger or healthier patients. We must redouble our efforts to hit this target by appropriately using all our weapons: weight control, exercise, oral hypoglycemic drugs and insulin therapy.

Ken Flegel MDCM MSc
Senior Associate Editor, *CMAJ*
With the Editorial-Writing Team (Paul C. Hébert MD MHSc, Matthew B. Stanbrook MD PhD, Noni MacDonald MD MSc, Amir Attaran LLB DPhil and Laura Eggertson BA)

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