Is tight glycemic control in type 2 diabetes really worthwhile?

NO

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A 78-year-old inpatient in the rehabilitation ward has recently undergone a below-knee amputation for a gangrenous foot, a complication of type 2 diabetes. His hemoglobin A_{1c} (HbA_{1c}) values have never exceeded 7.5% and are usually less than 7%. A stroke last year left him dysphasic. He has never had a coronary event. A visitor has taken him for a much-appreciated dose of fresh air and sunshine. Upon returning to the ward, a nurse chides them both for missing a scheduled (4 times daily) capillary blood glucose measurement: "Don't you want to get better?" The result of the test is 5.6 mmol/L—euglycemic, as always. The experience transforms a rare moment of joy into sadness and worry.

A woman in her late 60s struggles to meet the glycemic targets set by her doctor. Her HbA_{1c} levels rarely dip below 8%; however, despite a carefully crafted combination of isophane insulin and insulin lispro twice daily at meals, she has frequent hypoglycemic reactions and continues to gain weight. The situation leaves her feeling fearful and discouraged.

A lean, 50-year-old truck driver was recently diagnosed with type 2 diabetes. He lives pay cheque to pay cheque. His 7-year-old grandson is the light of his life. The boy's mother is single and on welfare. The grandfather has been instructed to self-monitor his blood sugar 4 times daily, but the cost is $90 per 100 test strips. He would rather buy skates for the boy, but believes he must choose between maintaining his own health and assisting his struggling family.

The most recent edition of the Canadian Diabetes Association clinical practice guidelines suggests that most type 2 diabetes patients should aim to achieve an HbA_{1c} level of 7% or lower.[1] According to the guidelines, "all who are able" should be taught self-monitoring of blood glucose. For those not taking insulin, frequency of self-monitoring of blood glucose can be individualized, but should include "both preprandial and postprandial measurements."[1]

A painting illustrating the practice of uroscopy in the 17th century, by David Teniers the Younger. ©Royal Museum of Fine Arts of Belgium, Brussels. Used with permission.

With rare exceptions, type 2 diabetes does its harm over the course of many years. Its natural history varies widely among sufferers. Only massive prospective studies conducted over extended periods of time can shed meaningful light on this debate question. Considering prohibitive costs and logistical challenges, few such studies have been done. Inevitably, most of the Canadian Diabetes Association clinical practice guideline recommendations are based on expert consensus.

Evidence lacking

All science is tentative. Four studies currently provide most of what we think we know about glycemic goals in type 2 diabetes.

In the 1998 UKPDS (United Kingdom Prospective Diabetes Study),[2] relatively young (aged 25 to 64 years) new diabetes patients were randomized

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to "conventional" treatment (treatment by diet alone, with medications added if fasting plasma glucose levels exceeded 15 mmol/L or if symptoms developed) or "intensive" treatment (treatment targeted at euglycemia from the outset). Glycemic control over a 10-year period was better for the intensive treatment group than the conventional treatment group: mean HbA_{1c} values were 7% versus 7.9%, respectively. (These were new diabetes patients—by the end of the study, mean HbA_{1c} levels were 8.1% versus 8.7%, respectively). The result: a reduction in microvascular end points almost entirely accounted for by decreased retinal photocoagulation. There was no difference in mortality, macrovascular events, renal failure, or blindness.

In 2008, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study group[3] randomized 10251 patients (mean HbA_{1c} level at baseline was 8.1%) to their version of "intensive" therapy (target HbA_{1c} level of 6.0%, with 6.4% achieved) or "standard" therapy (mean HbA_{1c} level of 7.5%). The trial was halted after about 3.5 years because mortality in the "intensive" group was higher: 5% versus 4% (P=.04).[3]

Almost simultaneously, the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) group[4] randomized 11 140 patients and achieved mean HbA_{1c} values of 6.5% ("intensive" treatment) versus 7.3% ("standard" treatment). After 5 years, there was no difference in all-cause mortality, major macrovascular events, or retinopathy. The intensive treatment group had fewer new or worsening cases of proteinuria compared with the conventional treatment group (2.9% vs 4.1%). The group noted "a trend toward" reduced renal replacement or death from renal causes (0.4% vs 0.6%, P=.09), but these were rare events. There was no difference in the rate of doubling of serum creatinine.

Most recently, in 2008, the UKPDS returned with a 10-year posttrial, nonrandomized follow-up of surviving participants from the 1998 study.[5] Differences in glycemic control quickly disappeared with the termination of the trial—overall mean HbA_{1c} values were about 8%. However, differences emerged among the earlier treatment groups. With up to 10 years posttrial monitoring, patients treated "intensively" when first diagnosed were at lower risk of dying, suffering myocardial infarction, or (in the insulin-sulfonylurea group) having microvascular disease, defined as suffering vitreous hemorrhage, retinal photocoagulation, or renal failure. Absolute risk reduction was in the range of 3 to 4 events per 1000 patient-years (annual number needed to treat = 285). There was no difference in the rate of stroke or peripheral vascular disease. Metformin use was associated with lowered risk ratios for death and myocardial infarction, but not reduction in microvascular complications.

Does "tight control" in diabetes management really help our patients? Those in the "intensive" groups studied were consistently more likely to suffer hypoglycemic reactions, be hospitalized, and gain weight. Initial costs for patients and society are inevitably higher, and studies reveal that self-monitoring is generally of no benefit to stable type 2 diabetes patients not taking insulin[6] and that it negatively affects quality of life.[7]

Bottom line

The bottom line: we have limited evidence of modest benefit at something less than "tight control" (and, with ACCORD, the possibility that "really tight" might be dangerous[3]). Is it worth it? Surely patients should be making that decision. This culture of "tight control" imposed by physicians in patient scenarios like those recounted above is not supported by empiric evidence.[8] For ethical reasons, we should be seeking ways to communicate our present knowledge to patients with more honesty and greater balance.

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Competing interests
None declared

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CLOSING ARGUMENTS

- Our culture of "tight control" in diabetes management too often tyrannizes patients, with little gain.
- The current literature is ambiguous regarding the benefits of tight glycemic control, with results ranging from increased mortality to modest improvement for a subset of clinically important end points.
- No trial has demonstrated reduced rates of stroke or peripheral vascular disease, nor is there empiric evidence to support self-monitoring for stable type 2 diabetes patients not taking insulin.
- Patients deserve to know the ambiguity of the evidence and to receive more support to make choices that reflect what they value.