Glycaemic control: do no harm

Kelly L, MD, MClinSci, CFPC
Professor. Division of Clinical Sciences, Northern Ontario School of Medicine, Canada
Correspondence to: Len Kelly, e-mail: lkelly@mcmaster.ca
Keywords: type 2 diabetes, glycaemic control, management

Peer reviewed. (Submitted: 2011-01-31. Accepted: 2011-04-23.) **S Afr Fam Pract 2012;54(1):6-7**

Tight glycaemic control for type 2 diabetes (T2DM) has always been a tough sell. It is rarely achieved safely, owing to noncompliance and hypoglycaemic episodes, and there has been little evidence to support it. New studies now speak of its potential harm.

The initial United Kingdom Prospective Diabetes Study (UKPDS) in 1998 was widely interpreted as evidence for tight glycaemic control, then defined as a haemoglobin A1c value of 7.0%.[1] In fact, in this trial no reduction was demonstrated in serious clinical episodes, i.e. macrovascular events (stroke or myocardial infarction). The often quoted 22% relative risk reduction in microvascular events (renal, ophthalmic, foot) actually referred primarily to a decreased need for retinal photocoagulation. However, there was no effect on visual acuity or renal failure.[1]

The one important item we learned from an arm of the UKPDS trial was that the use of metformin decreased mortality, independent of its hypoglycaemic effects.[2] Ten years later there is no other therapy that can claim such success.

Recently, several studies have added to our understanding of T2DM and the minimal microvascular benefits of tight glycaemic control, now defined as an A1c of 6.5% or lower.[3-5] However, this is overshadowed by present concerns of increased mortality[4] as hypoglycaemia continues to be an issue, with a two- to threefold increased incidence at lower A1c values.

The Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR) multicentre trial of 6 104 intensive care unit (ICU) patients demonstrated increased mortality in those whose sugar levels were kept between 4.5 and 6.0 mmol/l.[3] Compared to patients kept "under 10", tight glycaemic control led to an absolute increase in mortality of 2.6% [95% confidence interval (CI), 0.4–4.8].

A 2009 meta-analysis of 26 studies (including the previous one) involving 13 500 ICU patients concluded that intensive glycaemic control "conferred no overall mortality benefit among critically ill patients."[6] However, it did significantly increase the risk of hypoglycaemia (sixfold) even in these closely monitored patients.

How has tight glycaemic control affected ambulatory patients? In 2008, two studies looked at achieving an A1c of less than 6.5 mmol/l. The Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) trial introduced rosiglitazone, a thiazolidinedione.[4] The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study introduced gliclazide, a sulfonylurea.[5] Both studies used agents that were added to other medications, including metformin and insulin.

The ADVANCE trial followed 11 000 patients over five years and demonstrated a "21% relative reduction in nephropathy."[4] It specifically found that the development of macroalbuminuria was lower in the intensively treated group, at 2.95 vs. 4.10% (95% CI, 0.57–0.85). Clinically there was no statistically significant increase in renal dialysis or renal deaths.[4] This delay in worsening proteinuria was accompanied by a twofold increase in hypoglycaemic events, including some requiring hospitalisation. There was no beneficial effect on macrovascular events or death.[4]

The ACCORD study did find increased mortality with tight glycaemic control.[5] It followed 10 000 patients for 3.5 years and terminated the trial as a result of higher death rates associated with lower A1c measurements (hazard ratio, 1.22; 95% CI, 1.01–1.46). Intensively controlled patients also had a threefold increase in hypoglycaemic events (16% vs. 5%), and one quarter of them gained more than 10 kg in weight.[5]

A recent commentary in the Annals of Internal Medicine suggests that "interventions that overwhelm patients'

capacity to cope clinically, psychologically and financially, need to change."[7] Its authors suggest that "A1c levels between 7.0 and 7.5% seem reasonable and feasible for many patients."[7]

What about our elderly patients? The studies point out that the risk of hypoglycaemic events outweighs the changes in surrogate endpoints. Tight glycaemic control renders no statistically significant reduction in important clinical endpoints, including dialysis, stroke, myocardial infarction or death. Keeping hypoglycaemia at bay should be one of our primary concerns, as well as limiting the effects of hyperglycaemia. An A1c value of 7.0 or below is associated with a greater risk of falling.[8] Diabetes guidelines in Nova Scotia, Canada for extended care residents in long-term facilities consider random blood glucose values of between 10.0 and 15.0 mmol/l as acceptable, and even higher unless there are reversible symptoms.[9]

The only proven strategy for reducing macrovascular events in T2DM patients is blood pressure control, often requiring three or more medications.[10] A focus on exercise, diet and smoking cessation is far more important that glycaemic control, and this is confirmed by the literature.[11-13]

A simple approach to T2DM therapy is to ensure aggressive blood pressure control. I introduce metformin gradually up to its maximal tolerated dose. If the A1c remains high, I add NPH insulin and increase that with no upper limit in a once-daily or twice-daily dosing. My hope is to achieve a fasting morning glucose level lower than 10.0 mmol/l. If A1c is below 7.0% and the patient is only on metformin, I have no concern, as this is often a patient who has taken lifestyle changes seriously. If, however, the patient is on a therapy that can cause hypoglycaemia (insulin or other oral agents associated with hypoglycaemia), I always reassess the therapy and usually back off. I never use two agents that can cause hypoglycaemia simultaneously. Older patients teach me that they are more interested in their quality of life and I accept an A1c between 7.0% and 8.0% or higher if that is the best we can do.

We have to remember that we are treating the whole patient, some who live far from medical care, some who drive commercial vehicles, many who have other social and medical challenges. How would a severe hypoglycaemic attack affect them? The decision is not what laboratory value we strive for, but how safely we get there. If we do not keep it simple, one of us, either the patient or the physician, will not be able to keep up. It is not surprising that primary care surveys identify that we achieve glycaemic guidelines less that 50% of the time.[13] While this would seem to imply neglect or suboptimal care, is that in fact the case? Is it not maybe a reflection of the complex nature of what is primarily a lifestyle disease?

References

1. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:837–853.
2. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet 1998;352:854–65.
3. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009:360:1283–1297.
4. Patel A, MacMahon S, Chalmers J, Neal B, et al. Intensive blood glucose and vascular outcomes in patients with type 2 diabetes. NEJM. 2008;358:2560–2572.
5. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med. 2008;358:2545–2559.
6. Griesdale DE, De Souza RJ, Van Dam RM, et al. Intensive insulin therapy among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180:821–827.
7. Montori VM, Fernandez-Balsells M. Glycemic control in type 2 diabetes: time for evidence-based about face? Ann Intern Med. 2009;150(11):803.
8. Nelson J, Dufraux K, Cook P. The relationship between glycemic control and falls in older adults. J Am Geriatr Soc. 2007;55(12):2041–2044.
9. Mallery L. State of the art: diabetes guidelines for the elderly residents in long-term care facilities. Newsletter of the Diabetes Care Program of Nova Scotia 2009;19(1):1–2. Available from: http://www.diabetescareprogram.ns.ca/newsletter/2009/jan09.pdf
10. Alder AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000;321:412–419.
11. Perk J. Risk factor management: a practice guide. Eur J Cardiovasc Prev Rehabil. 2009;3(2):S24–8.
12. Mann D, Woodward M, Muntner P. Preventing diabetes complications: are we too glucocentric? Int J Clin Pract. 2010;64(8):1024-1027.
13. Mann D, Woodward M, Ye F, et al. Trends in medication use among US adults with diabetes mellitus: glycemic control at the expense of controlling cardiovascular risk factors. Arch Intern Med. 2009;169(18):1718-1720