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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

therapeutics letter

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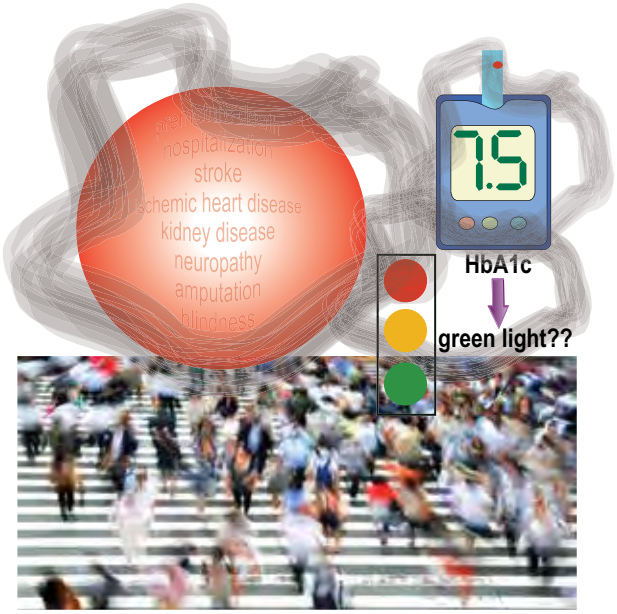
Is the current 'glucocentric' approach to management of type 2 diabetes misguided?



A recent Alberta modeling study suggests that lifetime risk of diabetes is now 50% for non-indigenous Canadians and 80% for First Nations Canadians.[1] If true, type 2 diabetes (DM2) will become the most common primary care diagnosis. Costs including medical visits, capillary blood glucose (CBG) testing, laboratory tests, and drug therapies will threaten other social priorities. In 2013, British Columbia spent over $52 million for CBG tests alone.[2] It is critical that the benefits of future therapy for this condition substantially outweigh the harms. However, there is a growing international recognition that the current 'glucocentric' approach (i.e. controlling blood glucose with multiple medications in patients without symptoms of hyperglycemia) may be misguided.

Therapeutics Initiative Letters

7 Therapeutics Letters (TL) relate to the management of DM2.

1998: TL 23[3] documented the drugs that were available in 1998 and noted "*there is no conclusive evidence that improved glucose control with oral agents leads to a decrease in the complications of type 2 diabetes*."

1998: TL 27[4] summarized the results of the United Kingdom Prospective Diabetes Studies (UKPDS). In one arm sulfonylurea or insulin was compared with diet and the only potential benefit of the drugs was a 2.4% reduction in retinopathy requiring photocoagulation. In contrast drug therapy increased major hypoglycemic episodes: diet 1%; chlorpropamide 4%; glyburide 6%; and insulin 23%. In a second arm of UKPDS, 1704 obese diabetic patients were randomised to metformin, diet or treatment with sulfonylurea or insulin. Metformin reduced mortality as compared to diet or drug therapy. We were aware of and commented on a third arm that showed that metformin added to maximal sulfonylurea therapy was harmful. However, like most of the rest of world we focused on the positive arm and concluded "*For first-line type 2 diabetes therapy the benefit/risk ratio for metformin is many fold greater than that for sulfonylureas or insulin*."

2000: TL 36[5] reviewed rosiglitazone, a new drug for DM2, and concluded "*rosiglitazone improves some surrogate markers and worsens others*."

2008: TL 68[6] reviewed the trials testing lower glycemic targets in DM2 and concluded, "*The optimal glycemic target in patients with type 2 diabetes is unknown*."

2011: TL 81[7] reviewed self-monitoring of blood glucose (SMBG) in DM2 and concluded, "*Most non-insulin treated patients with DM2 do not require routine SMBG*."

2014: TL 92[8] documented the limitations and potential hazards of using surrogates, including glycosylated hemoglobin (A1C), an estimate of glucose blood levels in the last 3 months.

2016: TL 100[9] questioned the use of A1C as the basis of approval for non-insulin glucose lowering drugs.

Our research has led us to conclude that the 'glucocentric' approach to the management of DM2 is **probably not in the best interests of patients**.

Other analyses of the current evidence

2009: Endocrinologists from the Mayo Clinic concluded: "*Our review and critique of recent large randomized trials in patients with type 2 diabetes suggest that tight glycemic control burdens patients with complex treatment programs, hypoglycemia, weight gain, and costs and offers uncertain benefits in return*."[10]

2011: A systematic review showed that when intensive glucose lowering was compared with standard care **the magnitude of the harms outweighed the benefits**.[11]

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2011: Leading diabetes experts argued in the British Medical Journal that **our obsession with A1C as a surrogate is damaging patient care**.[12]

2016: Researchers conducted a systematic review of metformin documenting that the cardiovascular and mortality benefit of metformin seen in one arm of UKPDS was contradicted in another arm of the same trial, not seen in any other RCTs and has never been replicated.[13]

2016: Researchers reviewed practice guidelines from 2006 to 2015 and compared them with meta-analyses and individual RCTs comparing glycemic targets.[14] The authors examined outcomes that "*patients experience and consider important*". Microvascular outcomes were: end-stage renal disease or dialysis, renal death, blindness and clinical neuropathy. Macrovascular outcomes were: all-cause mortality, cardiovascular mortality, fatal and nonfatal myocardial infarction (MI), fatal and nonfatal stroke, and peripheral vascular events or amputations. The authors concluded that "*evidence accrued in the past 2 decades consistently demonstrates no significant benefit of tight glycemic control on patient-important micro- and macrovascular outcomes*". Furthermore they note that "*most published statements and all guidelines unequivocally endorse tight glycemic control to prevent microvascular complications*". They emphasize the discordance between research evidence and guidelines for DM2 and conclude that it is time for us to rethink our approach.

2017: An evidence based analysis of DM2 RCTs questions the likelihood that an individual patient will benefit from treatment of DM2 over an expected life span and suggests we balance this against the inevitable burdens and harms of treatment. The authors conclude: "*Current evidence strongly supports that there is a potential epidemic of overtreatment with antihyperglycemic therapies in diabetes*."[15]

2017: The perspective in TL 100[9] is shared by cardiology and endocrinology experts at Yale: "*Trials that use outcomes based solely on glycemic parameters are no longer acceptable for clinical decision making. Clinicians and patients need evidence about outcomes associated with different drug classes and likely with different agents within a class. Investments in pragmatic studies of existing agents are needed to understand the impact on outcomes of all treatment options*."[16]

What is needed now?

The only way to improve the management of DM2 is to conduct trials that will answer the questions important to patients. Patients expect treatment that is proven to maintain healthy function, prevent premature death, hospitalization, stroke, ischemic heart disease, kidney disease, neuropathy, amputation and blindness. **At the present time we do not have that proof for the 'glucocentric' approach or for any drug for DM2.**
Boussageon et al[13] are correct to push for large long-term independent trials, which test different approaches and drugs, and most critically, measure outcomes that are important to patients. While we await the trial evidence, it is rational to emphasize lifestyle measures in these patients: weight loss, low carbohydrate diets and exercise.

Conclusions

- The increasing prevalence of type 2 diabetes presents a serious challenge to society.
- **There is growing evidence that the 'glucocentric' drug management approach is misguided.**
- Large long-term randomized controlled trials measuring outcomes important to patients are needed urgently to test different approaches and drugs for the management of type 2 diabetes.
- **While waiting for the evidence, it makes sense to focus efforts and resources on lifestyle measures.**

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The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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