Pregnancy glycemia to vascular risk: Nonglycemic diabetes?

J. Kennedy Cruickshank MB MD, Moulinath Banerjee MD PhD

Previously published at www.cmaj.ca

∞∞ See related research article by Retnakaran and Shah, page 371

Does our concept of type 2 diabetes and its specialty practice need redirecting? Are the well-known vascular complications associated with type 2 diabetes mellitus because of subclinical damage that occurs long before hyperglycemia becomes apparent? Is this a case of the chicken or the egg[1] or of common soil?[2]

Twenty-five years ago, Jarrett[1] suggested that the standard causal pathway of elevated blood glucose leading to vascular injury was not so simple. Ten years later, he addressed gestational diabetes, commenting that "any maternofetal morbidity is more likely … due to maternal age or obesity or, indeed, to the effects and consequences of diagnosis than to the glucose intolerance."[3] Lessons from history may be relevant, with a paper from 60 years ago suggesting that "a metabolic disturbance in the mother was active (in gestational diabetes) for as long as 20 years before diabetes was diagnosed."[4] Ten years after Jarrett's 1984 paper, Stern[4] reformulated the problem as a "common soil" hypothesis, proposing that both vessel damage and hyperglycemia might have a common cause. To date, basic scientists and the world of clinical diabetes have not taken up that challenge seriously.

In this issue, Ratanakara and Shah[5] provide further evidence that diabetes begins as an early vascular problem. Using a large electronic database of patient records in Ontario, they showed that women tested for glycemia during pregnancy had more vascular events or died more quickly during the following 12 years than those who did not receive testing. The risk was not as great as for those labelled with gestational diabetes. The vascular damage in patients who are tested is subtle but clear when examined.[6] Unusually, the authors used the oldest group, women aged 45–49 years, as the reference group, so that vascular risk was linearly reduced in each 5-year age group below that. The 66% excess risk among those with gestational diabetes was paralleled by a 19% excess risk among those with presumed hyperglycemia. Absolute rates were very low in these relatively young women at 4.2, 2.3 and 1.9 per 10 000 person years for women with gestational diabetes, presumed hyperglycemia and untested women, respectively, thus the need for a large sample to show the effect. However, these differences rise over time and are expressed as clearly higher vascular mortality in such glucose intolerant people some 15 years later.[7] The authors did not have access to laboratory glucose values, but they astutely deduced that if the health care system was charged for more than 1 blood glucose test for the same pregnant woman in 1 day, the woman probably received a glucose tolerance test. Body mass index or an indication of obesity was also unavailable. Nevertheless, almost every other report worldwide has shown that women with gestational diabetes are more obese than women with intermediate results, who are more obese than normoglycemic women, as found in the Hyperglycemia and Adverse Pregnancy Outcomes study.[8] Therefore, women in both the marginal and overtly hyperglycemic groups in the present study were probably more obese than women with normoglycemia. Obesity (and its metabolic products) seems to be the key confounder of hyperglycemia as the direct cause of the excess cardiovascular events.

Key points

- Women screened for gestational diabetes but without overt diabetes have increased risk of vascular disease, however, the absolute risk is low.
- These results add weight to the debate over "the chicken, and the egg" and the "common soil" hypotheses about vascular disease and diabetes. That is, is type 2 diabetes a vascular disease before it becomes glycemia?
- Randomized trials of intensive glycemic control in type 2 diabetes for primary prevention of large or small vessel disease and premature mortality have not been successful and have increased obesity.
- Should type 2 diabetes be redefined as a vascular disease, with glycemia secondary to obesity?

The authors' analysis brings into question whether type 2 diabetes can still be defined as "just" hyperglycemia, that is as a blood glucose level above which retinopathy (in the original Pima Indian cohorts[9]) first becomes excessive. As vessel disease causes trouble well before excess glucose is detectable, a new definition of type 2 diabetes will need to incorporate earlier blood vessel damage rather than or as well as glycemia. The remarkable failure of hyperglycemic management to reduce mortality or improve event rates in trials of

J. Kennedy Cruickshank and Moulinath Banerjee are with the Department of Cardiovascular Sciences, Manchester Royal Infirmary, University of Manchester, Manchester, UK

Cite as *CMAJ* 2009. DOI:10.1503/cmaj.091396

DOI:10.1503/cmaj.091396

treatment of type 2 diabetes conducted over a period of 40 years[10,11] suggests that current glycemic treatment is not a long-term solution — and, as a test of causality, that glycemia might not be the basic cause of diabetic disease. What is confusing to generalists is distinguishing between "reasonable" and intensive glycemic control as is now promoted. "Reasonable" is not based on evidence but on common sense and is important to prevent osmotic symptoms, such as polyuria, genital irritation, tendency to infections and poor wound healing. In women with known type 2 diabetes, tighter preconceptional glycemic control is as vital for women with gestational diabetes, not for the mother's physical health but to prevent congenital malformations and inappropriate growth of the fetus.

Perhaps the cause of the failure of intensive glycemic control regimens, particularly insulin, sulphonylureas and glitazones, is that they inevitably increase weight in already obese people, by an average of 6 kg in the UKPDS trial,[12] which is frequently cited as showing the benefits of intensive insulin control. Metformin is the exception but not when combined with sulphonylureas. That trial's much-trumpeted microvascular gain was not impressive, if present at all after events in the hypertension arm are excluded. The absolute microvascular risk reduction from intensive glycemic control in this trial was only 2.8 events per 1000 people; thus, 357 patients would need to receive treatment for 1 year to avert 1 event, or 36 people for 10 years. The recent claim that patients should wait 17 years for a 9% relative overall benefit is surely clutching at glycemic straws.[13] The Advance trial's retinopathy substudy has not fared much better, despite its parent Advance trial averaging some 30 visits in the intensive control arm compared with 7 in the control arm.[14]

Weight gain may be key. The newer incretin-like agents (derived from gut hormones supressing glucagon and allowing improved insulin action) can now be trialed to test whether weight gain has been the cause of glycemic control's failure to prevent vascular disease so far. We must still wait to see whether these drugs do more harm than good. Despite any condition caused by excess energy intake and reduced expenditure (less physical activity) likely being resistant to pharmacological treatment, the next generation of agents should focus on the blood vessel rather than on glycemia. Perhaps the focus of diabetes research on insulin resistance has been misdirected. There is little doubt that insulin resistance is secondary to fat storage in any affected tissue, so attempts to reverse such resistance pharmacologically may not work. What the study by Retanakara and Shah shows is that we all have a great deal to learn from subclinical blood vessel changes in younger women who are likely overweight during pregnancy. Is their glycemia relevant? Those who study diabetes must wrestle constructively with this question, or the current concepts may become redundant.

Competing interests: None declared.

Contributors: Both of the authors drafted the commentary, revised it critically and approved the final version submitted for publication.

REFERENCES

1. Jarrett RJ. Type 2 (non-insulin-dependent) diabetes mellitus and coronary heart disease — chicken, egg or neither? *Diabetologia* 1984;26:99-102.
2. Stern MP. Diabetes and cardiovascular disease. The "common soil" hypothesis. *Diabetes* 1995;44:369-74.
3. Jarrett RJ. Gestational diabetes: a non-entity? *BMJ* 1993;306:37-8.
4. Gilbert JAL, Dunlop DM. Diabetic fertility, maternal mortality, and foetal loss rate. *BMJ* 1949;1:48-51.
5. Retanakara R, Shah BR. Mild glucose intolerance in prenancy and risk of cardiovascular disease: a population-based cohort study. *CMAJ* 2009. DOI:10.1503cmaj .090569.
6. Banerjee M, Cruickshank JK. Pregnancy as the prodrome to vascular dysfunction and cardiovascular risk. *Nat Clin Pract Cardiovasc Med* 2006;3:596-603.
7. Cruickshank K, Riste L, Anderson SG, et al. Aortic pulse-wave velocity and its relationship to mortality in diabetes and glucose intolerance: an integrated index of vascular function? *Circulation* 2002;106:2085-90.
8. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, et al. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 2008;358:1991-2002.
9. World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus.* Geneva (Switzerland): The Organization; 1999.
10. Knatterud GL, Klimt C, Levin ME, et al. Goldner MG for the University Group Diabetes Program, UGDP. Effects of hypoglycaemic agents on vascular complications in patients with adult-onset diabetes. VII. Mortality and selected non-fatal events with insulin treatment. *JAMA* 1978;240:37-42.
11. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
12. 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;352:837-53.
13. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359:1577-89.
14. Beulens J, Patel A, Vingerling J, et al. Effects of blood pressure lowering and intensive glucose control on incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. *Diabetologia* DOI 10.1007/s00125-009-1457-x. Epub 2009 July 25 ahead of print.

Correspondence to: *Dr. J. Kennedy Cruickshank, Professor of Cardiovascular Medicine & Clinical Epidemiology, Manchester Royal Infirmary, 3rd Fl., University of Manchester, 46 Grafton St., Manchester M13 9NT UK; fax 0161-275-1183; kennedy.cruickshank@manchester.ac.uk*