Cardiovascular risk and glycemic control

Alice Y.Y. Cheng MD, Lawrence A. Leiter MD

See related research paper by Ko and colleagues, page 919

The use of a multifactorial approach to the treatment of diabetes mellitus is associated with dramatic reductions in both macrovascular and microvascular complications of diabetes.[1,2] Nevertheless, intensive glycemic control, with a target hemoglobin A_{1c} level of less than 6%–6.5%, has not been found to show cardiovascular benefits in 3 recent trials.[3–5] Intensive therapy was even associated with a small increase in mortality in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[3] a finding that led to the premature discontinuation of the glucose component of the trial. Fortunately, this was not observed in the 2 other major trials. However, such findings raise the question of whether some of the glucose-lowering treatments used in the studies, including insulin, may have increased, rather than decreased, cardiovascular risk.

It is essential to place such findings in their proper context. The median length of follow-up in these 3 trials was 3.5–5 years. The participants involved had advanced diabetes at the outset, with an average duration of disease of 8–11 years. Questions about the importance of the timing of glycemic intervention were raised recently by the findings of the 10-year post-trial follow-up of the United Kingdom Prospective Diabetes Study (UKPDS).[6] In the original study, the risk of microvascular complications decreased by 25% among patients with newly diagnosed type 2 diabetes who received intensive therapy,[7] whereas the risk of myocardial infarction and mortality did not decrease. In the 10-year follow-up of participants in the UKPDS study, the risk of microvascular complications continued to decrease by 24%, and the risk of myocardial infarction decreased by 15% and all-cause mortality by 13%. The mean hemoglobin A_{1c} level during the follow-up period was the same in the treatment and control groups.

Glycemic control instituted early in the course of type 2 diabetes thus appears to have a "legacy effect" (or "metabolic memory") whereby reductions in the risk of microvascular complications are seen early and persist over time and reductions in the risk of macrovascular complications may take years to manifest. A similar phenomenon was observed among patients with type 1 diabetes in another post-trial follow-up study.[8] This apparent legacy effect raises the possibility that the degree of glycemic control does indeed play a role in reducing the risk of cardiovascular complications of diabetes but that glucose-lowering therapy needs to be administered early in the course of the disease and that benefits become evident only after a long period. Greater reductions in cardiovascular events were also observed among participants with no prior cardiovascular disease and those with a baseline hemoglobin A_{1c} concentration of 8% or less in a prespecified subgroup analysis of the ACCORD trial. This finding, too, supports the hypothesis that earlier glycemic intervention is associated with greater cardiovascular benefit.

Key points

- Intensive glucose-lowering therapy has not been shown to reduce cardiovascular events over the short term among patients with a long duration of type 2 diabetes mellitus.
- Intensive glycemic control instituted early in the course of the disease may have long-term cardiovascular benefits.
- High levels of C peptide are a marker of increased insulin resistance, which is associated with other metabolic disturbances and increased risk for cardiovascular disease.
- The individual clinical situation and degree of glycemic control, rather than the C peptide level, should be considered when deciding whether to treat type 2 diabetes with insulin.
- A multifactorial approach to diabetes treatment is imperative to reduce the risk of micro- and macrovascular complications of diabetes.

In this issue of *CMAJ*, Ko and colleagues[9] report the results of a longitudinal cohort study that examined whether treatment with insulin is related to an increase in risk of cardiovascular disease or death among some patients with type 2 diabetes. The authors studied outcomes among participants who received phenotype-targeted therapy based on their fasting C peptide level, which is a marker of endogenous insulin production. After a follow-up period of 9 years, the incidence of cardiovascular disease and mortality were lower in the group receiving phenotype-targeted therapy than in the group receiving non-phenotype-targeted therapy. After age, sex and disease duration were controlled for in the model, however, the difference between groups was no longer significant. The authors suggest that, because the worst outcomes occurred among patients receiving insulin who had normal to high C peptide levels (i.e., high endogenous insulin secretion), these patients should not receive insulin therapy.

This study has many redeeming aspects, including complete and reliable data collection and rigourous statistical analyses. But its conclusions must be interpreted cautiously. The question of whether exogenous insulin therapy is related to increased risk of cardiovascular events was previously put to rest by several studies, particularly the UKPDS. Such stud-

Alice Cheng and Lawrence Leiter are with the Division of Endocrinology and Metabolism, St. Michael's Hospital, and the Department of Medicine, University of Toronto, Toronto, Ont.

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ies showed that better glycemic control with either insulin or sulphonylurea drugs was associated with a reduced risk of microvascular complications and no increase in risk of macrovascular complications.[6,7]

Elevated endogenous insulin levels represent a compensatory response to insulin resistance, which is associated with numerous metabolic disturbances. These disturbances are known to increase the risk of cardiovascular events and include elevated blood pressure, dyslipidemia, endothelial dysfunction, increased inflammatory and prothrombotic factors and microalbuminuria.[10] The findings of Ko and colleagues support the evidence for an association between insulin resistance and these clinical conditions. Study participants who had high C peptide levels also had lower baseline levels of high-density lipoprotein levels and higher baseline blood pressure, triglyceride levels, weight and waist circumference. Also, those in the insulin-treated, high-C-peptide group had worse glycemic control, longer duration of diabetes and more microvascular complications at baseline compared with the patients in the other groups. It is therefore not surprising that these baseline characteristics were associated with worse outcomes. In fact, the analysis by Ko and colleagues supports the alternate interpretation that the higher incidence of cardiovascular disease in the insulin-treated, high-C-peptide group was due to other metabolic factors. After control for confounders, only age, duration of diabetes and albuminuria were independent predictors for all-cause mortality, and only age, male sex, estimated glomerular filtration rate and albuminuria were independent predictors for cardiovascular disease.

Phenotype-targeted therapy to specifically address the abnormalities of individual patients is an appealing notion. But its applicability has not been established. In a disease as complex as type 2 diabetes, every deficiency is associated with many other metabolic disturbances. It is therefore a challenge to isolate one marker or one ideal therapy. Rather than predicting the effectiveness of insulin therapy, elevated C peptide levels merely help to identify the insulin-resistant patient, who usually can be easily distinguished clinically.

Insulin should be initiated at any point in the management of type 2 diabetes to achieve better glycemic control. It may be better to do so early in the course of the disease, since early glycemic control may carry the most benefit. The evidence to date is not sufficient to support clinical use of C peptide levels as a reliable method of differentiating those who would benefit from insulin therapy from those who would not. However, when managing type 2 diabetes, clinicians should keep in mind that glycemic control is only one part of a multifactorial approach to the reduction of microvascular and macrovascular complications.

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Correspondence to: *Dr. Alice Y.Y. Cheng, 507–2300 Eglinton Ave. W, Mississauga ON L5M 2V8; fax 905 828-7769; chenga@smh.toronto.on.ca*