

# The Irrefutable Importance of Glycemic Control

Reviewed by Yasser Ousman, MD, and Meeta Sharma, MD

## STUDY

Stratton IM, Adler AI, Andrew H, Neil W, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR (on behalf of the U.K. Prospective Diabetes Study Group): Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000

## SUMMARY

**Objective.** To determine the relationship between exposure to glycemia over time and the risk of macrovascular and microvascular complications in patients with type 2 diabetes.

**Design.** A prospective observational study.

**Subjects.** A total of 4,585 white, Asian Indian, and Afro-Caribbean United Kingdom Prospective Diabetes Study (UKPDS) patients, whether randomized or not to treatment, were included in analyses of incidence. Of these, 3,642 were included in the analysis of relative risk.

**Outcomes measured.** Primary predefined aggregate clinical outcomes: any end point or death related to diabetes and all-cause mortality. Secondary aggregate outcomes: myocardial infarction (MI), cerebrovascular accident, amputation, and microvascular disease. Single end points: nonfatal heart failure and cataract extraction. Risk reduction was associated with a 1% reduction in updated mean HbA<sub>1c</sub>, adjusted for possible confounders at diagnosis of diabetes.

**Results.** The incidence of clinical complications was significantly associated with glycemia. Each 1% reduction in

updated mean HbA<sub>1c</sub> was associated with reductions in risk of 21% for any end point related to diabetes ( $P < 0.0001$ ), 21% for death related to diabetes ( $P < 0.0001$ ), 14% for MI ( $P < 0.0001$ ), and 37% for microvascular complications ( $P < 0.0001$ ). No threshold of risk was observed for any end point.

**Conclusions.** The risk of complications in patients with type 2 diabetes is strongly associated with hyperglycemia. Any reduction in HbA<sub>1c</sub> is likely to reduce the risk of complications. Patients with HbA<sub>1c</sub> values in the normal range have the lowest risk.

## COMMENTARY

To date, the UKPDS is the largest prospective, randomized study involving patients with type 2 diabetes.<sup>1</sup> In the UKPDS, patients were initially randomized to intensive treatment with different anti-hyperglycemic agents versus conventional treatment using diet alone. During the course of the study, patients in the conventional treatment arm were switched to the intensive treatment arm if their fasting plasma glucose was  $>270$  mg/dl or if they had symptomatic hyperglycemia. At the end of the study, the intensive-treatment group achieved a median HbA<sub>1c</sub> of 7% versus 7.9% in the conventional-treatment arm. There was a significant reduction in microvascular complications and a borderline reduction in the risk of MI in favor of the intensive-treatment group.

The current study is an observational analysis of the UKPDS data intended to estimate the risk of complications at different levels of glycemia and to deter-

mine whether a threshold of glycemia exists. In other words, is there a concentration of blood glucose above which the risk of complications markedly increases? Do macrovascular and microvascular complications related to diabetes occur in a continuous relationship as a function of the degree of hyperglycemia? Also, at what level of glycemia, as reflected by mean HbA<sub>1c</sub>, do these complications start to occur?

To answer these questions, the investigators calculated an updated mean HbA<sub>1c</sub> for each patient by averaging the baseline HbA<sub>1c</sub> (at entry to the study) with the mean annual HbA<sub>1c</sub>. The updated mean HbA<sub>1c</sub> values were stratified into categories ranging from 4.6% to 11.2%. The rate of a given complication was then calculated for each category of updated mean HbA<sub>1c</sub>. Hazard ratios and relative risk were calculated before and after adjustments for other cardiovascular risk factors such as sex, age, ethnic group, smoking, HDL cholesterol, LDL cholesterol, triglycerides, albuminuria, and blood pressure.

The relative risk of a given complication for a given category of updated mean HbA<sub>1c</sub> was compared to the category with the lowest updated mean HbA<sub>1c</sub>, that is,  $<6\%$  (reference category). Follow-up was for 7.5–12.5 years.

This study clearly revealed that there is a direct relationship between the risk of complications of diabetes (microvascular and macrovascular) and the degree of hyperglycemia over time. There was no threshold of glycemia above which the risk of complications no longer increased, nor was there a threshold below which the risk no longer

decreased. The risk of each of the complications evaluated rose with increasing mean HbA<sub>1c</sub>. In particular, the risk of MI at near-normal mean HbA<sub>1c</sub> was two to threefold that of microvascular complications. These risks became equal at a higher HbA<sub>1c</sub>.

From another viewpoint, the researchers show a dramatic decrease in the risk of complications for each 1% reduction in mean HbA<sub>1c</sub> as follows: 21% reduction in any end point related to diabetes, 21% in death related to diabetes, 21% in all-cause mortality, 37% in microvascular complications, 43% in amputations and death from peripheral vascular disease, 14% in MI, 12% in stroke, and 16% in heart failure. Undoubtedly, these percentage reductions are epidemiological results. They are, however, comparable to data obtained from previous clinical trials conducted in patients with type 2 diabetes.<sup>1-4</sup>

There are several crucial implications for practitioners.

1. Even mild sustained elevations in HbA<sub>1c</sub>, as a reflection of overall blood glucose control, are associated with increased risks of complications and in particular the risk of MI.
2. Every effort should be made to lower HbA<sub>1c</sub>, because any reduction in HbA<sub>1c</sub> will translate into a reduction in the risk of complications.
3. The individuals who are most likely to benefit from risk reduction are those with the highest initial blood glucose values.
4. Physicians caring for patients with type 2 diabetes should aim for the best possible glycemic control. Unless contraindications exist, a near-normal or normal level of glycemia, as manifested in a normal HbA<sub>1c</sub>, should be the goal of diabetic therapy.

## REFERENCES

<sup>1</sup>UKPDS Study Group: Intensive blood glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837-853, 1998

<sup>2</sup>Klein R: Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care* 18:258-268, 1995

<sup>3</sup>Pirart J: Diabetes mellitus and its degenerative complications: a prospective study of 4,400 patients observed between 1947 and 1973 (Part 1). *Diabetes Care* 1:168-188, 1978

<sup>4</sup>Wei M, Gaskill SP, Haffner SM, Stern MP: Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. *Diabetes Care* 21:1167-1172, 1998

*Yasser Ousman, MD, is an endocrinology research fellow at MedStar Research Institute in Washington, D.C. Meeta Sharma, MD, is Associate Director of the Diabetes Team at MedStar Diabetes Institute at Washington Hospital Center in Washington, D.C.*