References

1. Bloomgarden ZT: Metformin. *Diabetes Care* 18:1078–1080, 1995
2. U.K. Prospective Diabetes Study Group: U.K. Prospective Diabetes Study Paper VIII: study design, progress and performance. *Diabetologia* 34:877–890, 1991
3. U.K. Prospective Diabetes Study Group: U.K. Prospective Diabetes Study 16: overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995

Threshold of HbA_{1c} for the Effect of Hyperglycemia on the Risk of Diabetic Microangiopathy

We previously reported the results of the Berlin Retinopathy Study, demonstrating a significant increase in the rate of background retinopathy from 1.64 to 4.31 per 100 patient-years around an HbA_{1c} of 9.0%, indicating a nonlinear relationship between the degree of hyperglycemia and retinal complications (1). Similarly, Krolewski et al. (2) reported recently that the relationship between glycemic control and microalbuminuria may follow a threshold model, showing a steep increase beyond an HbA_{1c} of 8.1%.

Practicing physicians are faced with the problem of applying these results to the long-term glycemic control seen in their patients. Current recommendations based on results of the Diabetes Control and Complications Trial (3) emphasize the aim of achieving HbA_{1c} values of ≤7%, and action should be taken when levels are >8.0% (high-performance liquid chromatography [HPLC], normal range 5.0 ± 0.5%) (4). The European IDDM policy group (5) defines the following targets: HbA_{1c} values <3 SD above the mean of healthy individuals indicate good control, 3–5 SD fair control, and >5 SD poor control.

To investigate whether the reference to the values of healthy control subjects is a useful tool to extrapolate the risk for complications, we conducted parallel determinations of HbA_{1c} in Berlin and at the Steno Diabetes Center of 225 children with IDDM who are part of the ongoing Berlin Retinopathy Study. Although, using similar assay procedures (HPLC, Biorad Diamat [Berlin] and Biorad Variant [Steno]), comparable normal ranges ($\bar{x}$ ± 2 SD; Berlin: 4.0–6.0%; Steno: 4.1–6.4%) and excellent correlation between results were obtained (r = 0.984; Fig. 1), the estimation of the percentage of patients in fair and poor control varied considerably. This was caused by a minor slope in the regression line, apparently due to slight variations in the assay conditions, which are relevant in particular in the higher readings obtained in patients with diabetes.

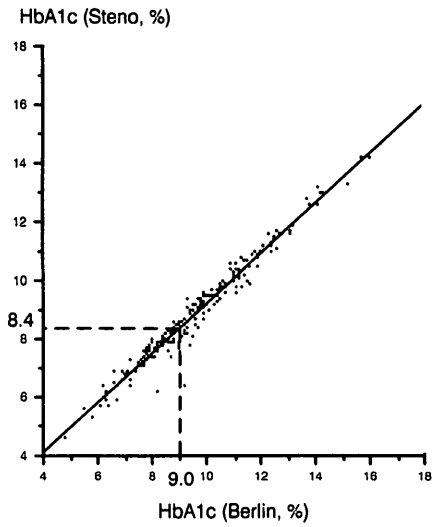

Figure 1—*Correlation between the HbA_{1c} values determined at Steno Diabetes Center and at the Berlin Children's Hospital indicating systematic discrepancies between centers despite similar HbA_{1c} methods and comparable normal ranges. The suspected threshold at an HbA_{1c} of 9.0% in Berlin corresponds to 8.4% at Steno.*

In these unselected children, satisfactory control (≤5 SD of normal) was reached by only 15% according to the Berlin results compared with 37% according to Steno. Interestingly, the threshold for retinopathy calculated from the long-term Berlin results of 9.0% would correspond to an HbA_{1c} of 8.4% at Steno (Fig. 1). This is close to the described threshold of 8.1% in the Joslin study, supporting the notion that a similar threshold may exist for microalbuminuria and retinopathy (6). In fact, the goal of an HbA_{1c} below the suspected threshold (9.0 or 8.4%, respectively) was reached by 46% of the patients in the Berlin Retinopathy Study.

Such comparative studies have proven to be necessary to compare the clinical outcomes of patient care in different institutions as a measure of quality control. In contrast, the exclusive calibration of HbA_{1c} values to the standard deviation range of control values may lead to clinically relevant wrong conclusions regarding the risk for microangiopathy.

Thomas Danne, MD
Bruno Weber, MD, FRCP
Bo Dinesen, MSC
Henrik B. Mortensen, MD

From the Children's Hospital (T.D., B.W.), Kaiserin Auguste Victoria Haus, Virchow-Klinikum, Humboldt University, Berlin, Germany; the Steno Diabetes Center (B.D.), Gentofte; and the Department of Pediatrics (H.B.M.), University of Glostrup, Glostrup, Denmark.

Address correspondence to Thomas Danne, MD, Kinderklinik, Virchow-Klinikum, Med. Fakultat der Humboldt Universitat Berlin, Augustenburger Platz, 13353 Berlin, Germany.

Acknowledgments— This investigation was part of the Hvidore Study Group On Childhood Diabetes, which receives financial support from Novo Nordisk.

References

1. Danne T, Weber B, Hartmann R, Enders I, Burger W, Hövener G: Long-term glycemic control has a nonlinear association to the frequency of background retinopathy in adolescents with type I diabetes: follow-up of the Berlin Retinopathy Study. *Diabetes Care* 17:1390–1396, 1994
2. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 332:1251–1255, 1995
3. DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
4. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 17:616–623, 1994
5. European IDDM Policy Group: *Consensus Guidelines for the Management of Insulin-Dependent (Type I) Diabetes*. Bussum, The Netherlands, Medicom Europe BV, 1993
6. Warram JH, Manson JE, Krolewski AS: Glycated hemoglobin and the risk of retinopathy in insulin-dependent diabetes mellitus. *N Engl J Med* 332:1305–1306, 1995