

## COMMENTS AND RESPONSES

### Flexible Intensive Insulin Therapy in Adults With Type 1 Diabetes and High Risk for Severe Hypoglycemia and Diabetic Ketoacidosis

Response to Sämman et al.

The recent subgroup analysis by Sämman et al. (1) examined the effectiveness of diabetes treatment and teaching programs (DTTPs) and advocated intensive insulin therapy combined with increased dietary freedom in individuals with type 1 diabetes who were at increased risk of hypoglycemia. There were significant reductions in hypoglycemic episodes, from 6.1 to 1.4 hypoglycemic events per patient per year, after participation. Sämman et al. concluded that DTTPs may reduce the occurrence of hypoglycemic episodes for those at risk, but, for several reasons, this conclusion is questionable.

As the authors noted, regression to the mean explained at least part of the observed reductions, since a subgroup with higher previous incidence of hypoglycemic episodes was analyzed. From statistical simulations of baseline results, a reduction from 6.1 to 4.7 (95% CI  $\pm 0.2$ ) hypoglycemic events per patient per year may be expected simply due to regression to the mean. Furthermore, there was selection during recruitment of the whole study cohort, as patients frequently experiencing hypoglycemia were preferentially referred from their general practitioners or diabetologists (2). Re-

gression to the mean would therefore explain an even greater reduction in the subgroup from 6.1 to  $<4.7$  hypoglycemic events per patient per year.

As Sämman et al. also noted, interviewer bias may have been a particular problem. Baseline recall was purely based on participant's memory of the previous year, which would be vulnerable to interviewer influence. Patients were better prepared for their 1-year follow-up but must have felt some pressure to report improvements to the research team, who were to present results at annual meetings.

It is difficult to distinguish to what extent hypoglycemic episodes were decreased by simply increasing the frequency of blood glucose testing. As stated by Sämman et al. (1), this clearly improves glucose control (3), and there may have been little additional improvement on hypoglycemia by DPPTs.

A group at high risk of hypoglycemia, the young and physically active (4), are not well represented in this cohort, and, as with other trials of this type (5,6), the average age of participants (38 years) was relatively high. In a younger age-group (mean age 27 years), the occurrence of hypoglycemic episodes increased threefold, while following an intensive insulin program (7) and a less intensive approach during exercise has recently been recommended (8) for younger individuals with type 1 diabetes.

In light of the currently available information, controlled studies of the impact of DTTPs on hypoglycemia are needed; this is especially so for the young and physically active.

MARY E. PENNANT, MMEDSCI  
MARK D. CHATFIELD, MSC  
W. ANDY COWARD, PHD  
LES J.C. BLUCK, PHD

From the Medical Research Council Human Nutrition Research, Cambridge, U.K.

Address correspondence to Mary Pennant, Medical Research Council Human Nutrition Research, Fulbourn Road, Cambridge, CB1 9NL, U.K. E-mail: mary.pennant@mrc-hnr.cam.ac.uk.

DOI: 10.2337/dc06-2234

© 2007 by the American Diabetes Association.

#### References

1. Sämman A, Muhlhauser I, Bender R, Hunger-Dathe W, Kloos C, Muller UA: Flexible intensive insulin therapy in adults with type 1 diabetes and high risk for severe hypoglycemia and diabetic ketoacidosis. *Diabetes Care* 29:2196–2199, 2006
2. Sämman A, Muhlhauser I, Bender R, Kloos C, Muller UA: Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. *Diabetologia* 48:1965–1970, 2005
3. Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W: Blood glucose awareness training (BGAT-2): long-term benefits. *Diabetes Care* 24:637–642, 2001
4. Briscoe V, Davis S: Hypoglycemia in type 1 and type 2 diabetes: physiology, pathophysiology, and management. *Clinical Diabetes* 24:115–121, 2006
5. Plank J, Kohler G, Rakovac I, Semlitsch BM, Horvath K, Bock G, Kraly B, Pieber TR: Long-term evaluation of a structured outpatient education programme for intensified insulin therapy in patients with type 1 diabetes: a 12-year follow-up. *Diabetologia* 47:1370–1375, 2004
6. DAFNE Study Group: Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. *BMJ* 325:746, 2002
7. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Research Group. *N Engl J Med* 329:977–986, 1993
8. Tsalikian E, Kollman C, Tamborlane WB, Beck RW, Fiallo-Scharer R, Fox L, Janz KF, Ruedy KJ, Wilson D, Xing D, Weinzimer SA, the Diabetes Research in Children Network (DirecNet) Study Group: Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. *Diabetes Care* 29:2200–2204, 2006