

COMMENTS AND RESPONSES

Glycemic Control and Hypoglycemia: Is the Loser the Winner?

Response to Perlmutter et al.

The editorial by Perlmutter et al. (1) in the October 2008 issue of *Diabetes Care* commented on the long-term effects of severe hypoglycemia and raised concerns about our study (2), which reported that within the cohort of subjects who entered the Diabetes Control and Complications Trial (DCCT) during adolescence, there was no relationship between subsequent episodes of severe hypoglycemia and cognitive performance measured ~20 years after study entry. Below, we outline their five major concerns and provide supporting information.

One concern of Perlmutter et al. was the exclusion of potential participants from the DCCT if they had a history of severe hypoglycemia, thus limiting generalizability. However, a history of severe hypoglycemia was not an absolute exclusion criterion for participation in the DCCT. Indeed, 24% of the 175 participants had previously experienced 1–5 episodes of severe hypoglycemia with loss of consciousness before entry into the DCCT.

The editorial by Perlmutter et al. also suggested that nonparticipation may have been due to cognitive deterioration or severe hypoglycemic events. However, the 56 nonparticipants remained active in the Epidemiology of Diabetes Interventions and Complications (EDIC) protocol, and data are available on their frequency of severe hypoglycemia. The frequency distribution of severe hypoglycemia episodes is similar between the 56 nonparticipants and the 175 participants (5 vs. 9%, respectively). Therefore, dropout due to cognitive deterioration is unlikely. A comparison of cognitive performance between baseline and DCCT year 5 for both groups showed the same scores on seven domains, with participants scoring modestly better only on problem solving ($P = 0.01$).

Perlmutter et al. asserted that baseline data for the dropouts would have been useful: There were no differences in de-

mographic or clinical characteristics between the 175 participants and the 56 nonparticipants at baseline. Complete baseline data are available upon request.

Perlmutter et al. also stated that our article was unclear regarding the ages of the individuals during each severe hypoglycemic episode: By EDIC year 12, there were 294 events in 87 subjects (33 events, ages 13–16 years; 71, 17–19 years; 152, 20–29 years; and 38, 30–39 years). As noted on page 1936 of our article, the timing of severe hypoglycemic events did not affect performance on any of the eight cognitive domains evaluated.

Finally, Perlmutter et al. expressed concern regarding the synergistic effects of hyperglycemia and hypoglycemia and stated that statistical support for these effects was not reported. The synergistic effects of hypoglycemia and hyperglycemia on cognitive function were evaluated using the interaction term in an ANCOVA model. We found no statistically significant effect.

In conclusion, our research question related to the long-term effects of severe hypoglycemic episodes on cognitive performance associated with intensive insulin therapy during the DCCT and post-DCCT period. Our results indicate that for patients similar to those of the DCCT adolescent cohort, intensive diabetes therapy can be implemented without undue concern for development of long-term cognitive deficits during the follow-up period. Despite this finding, intensive diabetes therapy must be practiced with caution because severe hypoglycemia can cause short-term cognitive impairment that affects ability to carry out daily activities and can lead to seizure or coma. Moreover, effects of hypoglycemia at a younger age were not assessed. In sum, the goal of achieving tight glycemic control while avoiding severe hypoglycemia is appropriate for adolescent patients.

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References

- Perlmutter LC, Flanagan BP, Shah PH, Singh SP: Glycemic control and hypoglycemia: is the loser the winner? *Diabetes Care* 31:2072–2076, 2008
- Musen G, Jacobson AM, Ryan CM, Cleary PA, Waberski BH, Weinger K, Dahms W, Bayless M, Silvers N, Harth J, White N, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group: Impact of diabetes and its treatment on cognitive function among adolescents who participated in the Diabetes Control and Complications Trial. *Diabetes Care* 31:1933–1938, 2008