ics: comparison of weight gain liabilities. *J Clin Psychiatry* 60:358–363, 1999
4. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P, Jayathilake K, Meltzer HY, Roth BL: H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* 28:519–526, 2003
5. Cohen D: Diabetes mellitus during olanzapine and quetiapine treatment in Japan (Letter). *J Clin Psychiatry* 66:265–266, 2005
6. Cohen D: *Diabetes Mellitus in Schizophrenia or Schizoaffective Disorder: An Iatrogenic or Endogenic Problem?* Haarlem, Netherlands. PhD thesis. University of Utrecht, Netherlands, 2006
7. Koller EA, Cross JT, Doraiswamy PM, Schneider BS: Risperidone-associated diabetes mellitus: a pharmacovigilance study. *Pharmacotherapy* 23:735–744, 2003
8. Dwyer DS, Pinkofsky HB, Liu Y, Bradley RJ: Antipsychotic drugs affect glucose uptake and the expression of glucose transporters in PC12 cells. *Prog Neuro-Psychopharmacol Biol Psychiatry* 23:69–80, 1999

Modeling Chronic Glycemic Exposure Variables as Correlates and Predictors of Microvascular Complications of Diabetes

Response to Dyck et al.

We read with interest the article by Dyck et al. (1), in which the authors described a chronic glycemic exposure variable (GE_i) in the Rochester Study. They examined GE_i and its individual components (A1C, duration, and age at onset) in terms of prediction/correlation with complications and concluded that GE_i is generally predicted better than its individual components (see Table 3 of ref. 1).

Dyck et al. compared their results with our previously published analyses (2) using a different chronic glycemic exposure variable, A_1 months, noting that (as also reported by the Diabetes Control and Complications Trial [3]) this combination variable did not predict better than its components (A_1 and duration). Our analytic approach, however, was different; we compared the fit of models, including the components to a model, with the composite alone. The differences in fit were small but favored the separate components. It would thus be interesting to compare the total R^2 of alternate models, one with GE_i and another with its components, in the current study. We suspect that, as in our case, differences would be small.

Another interesting issue is the use of "age at onset " and "duration" (1) together effectively defining age itself. Could any enhanced prediction be related to age itself? Inclusion of the partial R^2 for age in Table 3 (see ref. 1) would be useful.

Dyck et al. further suggested that differences between these studies may be explained by the "choice of patients" and differences in outcome assessment. As the Epidemiology of Diabetes Complications study (4) is comprised of community-treated type 1 diabetic individuals from a childhood-onset cohort shown to be epidemiologically representative of type 1 diabetes, selection bias was unlikely. However, the inclusion of type 2 diabetic subjects in the Rochester Study may have influenced results. Nevertheless, we agree that a continuous neuropathy outcome measure may be preferable and that this difference also may have contributed to the differences reported. Consequently, a comparison of A_1 months and GE_i would be more informative if performed for the outcome common to both studies (Diabetes Control and Complications Trial protocol neuropathy).

Finally, one motivation behind developing the A_1 month measure was to address whether a glycemic threshold exists above which complications develop. Were the authors able to examine this issue using GE_i? While unable to determine a clear threshold, we found that ~1,000 A_1 months were experienced before the advent of advanced complications. This translates to 42 years of A1C 2% above normal or 18 years at 5% above normal, which reflects another motivation for our chronic glycemic exposure variable—a clinically useful concept of risk.

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DOI: 10.2337/dc06-2143

References

1. Dyck PJ, Davies JL, Clark VM, Litchy WJ, Dyck PJB, Klein CJ, Rizza RA, Pach JM, Klein R, Larson TS, Melton LJ III, O'Brien PC: Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. *Diabetes Care* 29:2282–2288, 2006
2. Orchard TJ, Forrest KY, Ellis D, Becker DJ: Cumulative glycemic exposure and microvascular complications in insulin-dependent diabetes mellitus: the glycemic threshold revisited. *Arch Intern Med* 157: 1851–1856, 1997
3. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes* 44:968–983, 1995
4. Wagener DK, Sacks JM, LaPorte RE, MacGregor JM: The Pittsburgh Study of insulin-dependent diabetes mellitus: risk for diabetes among relatives of IDDM. *Diabetes* 31:136–144, 1982

Modeling Chronic Glycemic Exposure Variables as Correlates and Predictors of Microvascular Complications of Diabetes

Response to Orchard et al.

We are pleased to respond to the letter by Orchard et al. (1), especially since they first raised the following question: Do composite measures of chronic glycemia correlate or predict complications better than individual components? Orchard et al. reported evidence against the hypothesis, while we (2) reported evidence for the hypothesis. Having considered their suggestions, we offer an explanation for why their conclusions differed from ours.

Orchard et al. (3) compared the fit