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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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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

from two models, one consisting of only the composite and the other consisting of a regression model that included both components. The regression model is a linear combination of the two components in which the weights are chosen to obtain an optimal fit; thus, the regression model itself is a composite, though one in which the fit to the data should be better than A_1 months (which is exactly what they found).

Since comparing two composites was not the goal of our study (2), we approached the analyses differently. We developed one regression model including all variables that were significant in the multivariate modeling, including the composite as well as individual components, as candidates for the model. Each partial R^2 measures the explanatory value of the corresponding variable beyond the prediction already available from all the other variables in the model. Except for severity of retinopathy at baseline, we found that the composite was consistently the best predictor and that the individual components added little, if anything.

We agree that age at onset and duration added together equal the age of the patient at the time of study, although the appropriate weights for these two time periods in predicting the outcome may differ, and determining whether the weights significantly differ would be of interest. However, this was not a focus of our study.

We also agree that the patient population under study and the choice of outcomes to be analyzed can influence the results and that a continuous neuropathy measure is desirable. Although use of a common outcome measure would assist in comparing our results with those of Orchard et al. (3), such a comparison was not the focus of our study (2). Finally, determining the threshold of chronic glycemia, which induces complications, is a worthy goal, but before we do this we want to include studies of normal subjects and glucose-impaired individuals currently being studied.

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A Critical Appraisal of the Continuous Glucose–Error Grid Analysis

Response to Wentholt et al.

In a recent publication, Wentholt et al. (1) stated that their aim was to critically explore the continuous glucose–error grid analysis (CG-EGA) (2) and to compare it with traditional techniques using data previously reported from two sensors. As developers of the CG-EGA, we hoped that our method might stimulate a discussion on the important problem of the accuracy of continuous monitoring sensors (CGS); therefore, we read this critique with interest.

The methods used by Wentholt et al. (1) unfortunately failed to take into account the basic structure of CGS data, which represent time series (i.e., sequential readings that are ordered in time) (3). This structure leads to two fundamental requirements in their analysis. First, consecutive sensor readings taken from the same subject within a relatively short time are highly interdependent. Therefore, standard statistical analyses such as *t* tests, while appropriate for independent data points, will produce inaccurate results if applied to CGS data. Second, the order of the CGS data points is essential for clinical decision making. For example, the sequences 90 → 82 → 72 mg/dl and 72 → 82 → 90 mg/dl are clinically very different. Standard accuracy measures, such as the mean absolute deviation (MAD) used by Wentholt et al. (1), do not account for the data's temporal order; if reference-sensor data pairs are reshuffled, the MAD remains the same.

As a result, the primary statistical analysis used by Wentholt et al. is flawed, both to demonstrate significant differences between the sensors and to imply that CG-EGA is insensitive. The CGS data from 13 subjects were pooled to compare 2 MADs (15.0 ± 12.2 vs. 13.6 ± 10.2%). The result was reported as significant ($P = 0.013$), but for these highly overlapping MADs to differ statistically required a large number (>1,000) of degrees of freedom, which was calculated by pooling the total number of CGS data points (735 and 1,156) across all subjects. Such an approach led to inaccurate conclusions because there were only 13 independent subjects, and the data points within each subject were highly dependent. If the correct number of degrees of freedom is used, the MADs of the two sensors are not different ($P > 0.5$), which confirms the CG-EGA results showing no differences.

Other conclusions by Wentholt et al. also deserve comment. First, they stated that CG-EGA is time consuming. Indeed, analyses of temporal data are intrinsically more sophisticated than standard time-independent statistics, but such analyses are essential for this type of data. CG-EGA software is available. Second, Wentholt et al. stated that "poor accuracy rate is barely noticeable in the final CG-EGA outcome," implying that this result of the CG-EGA is incorrect. However, this result is not incorrect because better combined (rate and point) accuracy during hypoglycemia is observed with the sensor, showing poorer rate accuracy in this critical region. It is