Diabetes Distress but Not Clinical Depression or Depressive Symptoms Is Associated With Glycemic Control in Both Cross-Sectional and Longitudinal Analyses

Lawrence Fisher, PhD
Joseph T. Mullan, PhD
Patricia Arean, PhD
Russell E. Glasgow, PhD
Danielle Hessler, PhD
Umesh Masharani, MD

OBJECTIVE — To determine the concurrent, prospective, and time-concordant relationships among major depressive disorder (MDD), depressive symptoms, and diabetes distress with glycemic control.

RESEARCH DESIGN AND METHODS — In a noninterventional study, we assessed 506 type 2 diabetic patients for MDD (Composite International Diagnostic Interview), for depressive symptoms (Center for Epidemiological Studies-Depression), and for diabetes distress (Diabetes Distress Scale), along with self-management, stress, demographics, and diabetes status, at baseline and 9 and 18 months later. Using multilevel modeling (MLM), we explored the cross-sectional and longitudinal relationships of the three affective variables with A1C, the prospective relationships of baseline variables with change in A1C over time, and the time-concordant relationships with A1C.

RESULTS — All three affective variables were moderately intercorrelated, although the relationship between depressive symptoms and diabetes distress was greater than the relationship of either with MDD. In the cross-sectional MLM, only diabetes distress but not MDD or depressive symptoms was significantly associated with A1C. None of the three affective variables were linked with A1C in prospective analyses. Only diabetes distress displayed significant time-concordant relationships with A1C.

CONCLUSIONS — We found no concurrent or longitudinal association between MDD or depressive symptoms with A1C, whereas both concurrent and time-concordant relationships were found between diabetes distress and A1C. What has been called “depression” among type 2 diabetic patients may really be two conditions, MDD and diabetes distress, with only the latter displaying significant associations with A1C. Ongoing evaluation of both diabetes distress and MDD may be helpful in clinical settings.
an instrument that documents mood states but does not link or associate each with particular events or life circumstances, such as diabetes; and 3) as distress linked specifically to diabetes and its management assessed by diabetes-specific distress questionnaires (e.g., Problem Areas in Diabetes Scale [14] or Diabetes Distress Scale [15]). Unfortunately, distinctions among these three potentially different affective conditions often have not been made clear across studies; the term “depression” has often been used to refer to all three, and a large number of scales and measures have been used inconsistently to measure each. Consequently, a lack of clarity regarding what was being assessed and differences in the types of measures used have exacerbated the problems of exploring the relationship between depression and glycemic control.

In a three-wave, longitudinal, observational study of 506 type 2 diabetic patients, we sought to clarify the differences and similarities among these three approaches to defining and measuring depression and their interrelationships with glycemic control by examining the systematic covariation of all three with glycemic control in the same cross-sectional, prospective, and time-varying analyses. Using well-established measures of each, our goals were to clarify issues of definition to provide clearer targets for the development of appropriate interventions. Three research questions were posed: First, what is the concurrent, independent relationship between each of these three affective constructs and A1C (cross-sectional analysis)? Second, does the level or occurrence of any or all of these three at initial assessment significantly predict changes in A1C over subsequent study waves (prospective analysis)? Third, do fluctuations in any or all of these three correspond with fluctuations in A1C over study waves (time-varying analysis)? In addition, we explored the impact of patient demographics, diabetes status, medications, self-management behaviors, and extradiabetes stressors in each analysis.

RESEARCH DESIGN AND METHODS — Patients were identified from registries from four urban community-based medical groups and four diabetes education settings. After physician permission was obtained, patients received a letter, a screening phone call, and then a personal visit from a project staff member to introduce them to the study and collect informed consent. Inclusion criteria were type 2 diabetes, age 21–75 years, ability to read and speak English or Spanish fluently, no severe diabetes complications (undergoing dialysis or legally blind), and no diagnosis of dementia or psychosis. At the initial assessment (T1), patients participated in a 1.5-h visit that included questionnaires, physical measurements and interviews, a 150-item mail-back questionnaire, and forms for a visit to a local laboratory for collection of blood and urine specimens. Patients were contacted again 9 (T2) and 18 (T3) months later, at which time the same assessments were repeated. The mean between-wave interval was 9.1 months. Patients who met the criteria for affective or anxiety disorder and who were not being treated were referred to their physician. Approval was received by the institutional review board at the University of California, San Francisco and at each participating facility.

The dependent variable for all analyses was A1C. Patient demographics included sex, self-identified ethnicity (white or nonwhite), age, education (years), and time since diagnosis (years). Also collected were use of insulin (yes or no), BMI, number of complications, and number of comorbidities. Diet and exercise were measured by the Summary of Diabetes Self-Care Activities, which has demonstrated reliability and sensitivity to change over time (16). Patients reported the number of days in the past week that they followed their diet or exercise plans. Life stress unrelated to diabetes was assessed by the Negative Life Events Scale (17), based on a list of 22 potential stressful events, such as death of a friend or being a crime victim. Life context stressors have been shown to affect glucose levels (18) and self-management behavior (19), thus potentially affecting glycemic control over time.

MDD was assessed by the CIDI (11), a frequently used, reliable, structured diagnostic interview based on DSM-IV criteria. The time frame for MDD at T1 was occurrence during the past year and “since we saw you last” was used for T2 and T3. Depressive symptoms were assessed by the CES-D (13), a frequently used, reliable, continuous scale that assesses the number of days during the last week that each of 20 free-standing depressive symptoms occurred. Diabetes distress was assessed by the DDS (15), a continuous scale (α = 0.93) that assesses each of 17 items across six levels of severity of emotional, regimen-related, social, and medical care distress related to diabetes and its management.

Data analysis
We used multilevel modeling (MLM) (20) to assess the independent relationship among demographics, diabetes status, stress, self-management, the three affective variables, and baseline level and change in A1C across three assessments, covering 18 months. MLM accounts for correlations among nested responses in repeated-measures designs and maximizes efficiency by including all available information for each respondent, even if an assessment is missed. A distinctive feature of MLM is that it allows for an estimation of between-person and within-person models to test whether the effect of a predictor on an outcome varies by patient subgroup. Finally, it accommodates tests of time-varying covariates, reflecting how subgroups of variables change together over time.

We evaluated two preliminary models to provide information about the variability of A1C. An unconditional means model partitioned the total variance of A1C across people and waves into two pieces: the between-person and the within-person variance. An unconditional growth model further partitioned the within-person variance into two pieces: the estimated variance of the slope of change in A1C over time and other changes in A1C not related to time. We then examined three analytic models. First, we evaluated how baseline predictors were related to baseline levels of A1C (cross-sectional analyses) and second, how these predictors were related to linear change in A1C over time (prospective analyses). Third, we also explored a set of time-varying covariates: how changes in a predictor over time were related to changes in A1C over time. These models corresponded to the three research questions posed.

Time was centered at T1 and coded in years (0, 0.75, and 1.5). The natural log of A1C was used to normalize the residuals. Baseline predictor variables were centered at their grand means so that the estimates of the intercept and time were interpretable. There was no evidence of multicollinearity among the predictors. Estimates were obtained with Proc Mixed (SAS version 9.2) using full maximum likelihood and robust SEs (20). We also examined nonlinearities among the continuous variables and assessed a series of
interactions among the three affective variables, as well as between each with age, sex, time with diabetes, and insulin use: all were nonsignificant. We also explored the impact of use of psychotropic medication in all models: again, all were nonsignificant. At each stage, residuals were examined for normality and heterogeneity.

RESULTS

Preliminary analyses
Telephone screening identified 640 eligible individuals, and 506 of these completed the T1 assessment (79.0%) (Table 1). No significant differences were recorded between those who refused initially and those who participated on all major study variables.

Approximately 81% of patients completed all three study waves, 21 (4.2%) missed T2 only, 40 (7.9%) missed T3 only, and 34 (6.7%) missed both T2 and T3. Patients who completed all three waves were compared with patients who missed one or two waves on 28 variables. Those who missed a wave more often spoke Spanish than English (r = 0.09, P = 0.04) and had diabetes longer. Those with MDD, high depressive affect, or diabetes distress did not miss a wave or drop out more often than those without these conditions.

Concurrent relationships
All three affective variables were significantly intercorrelated at T1, although the relationship between CES-D and DDS (r = 0.48, P < 0.001) was notably higher than the relationship of these two variables with MDD (MDD with CES-D, r = 0.29, P < 0.001; MDD with DDS, r = 0.15, P < 0.001). Both CES-D (r = 0.14; P = 0.002) and DDS (r = 0.17; P = 0.001) were significantly correlated with A1C, whereas MDD was not (r = −0.05). Of the 12 other variables in the multivariate model (Table 2), 8 displayed significant zero-order correlations with A1C: race/ethnicity (r = −0.19, P < 0.001), age (r = −0.08, P < 0.05), education (r = −0.16, P < 0.001), time with diabetes (r = 0.27, P < 0.001), insulin use (r = 0.29, P < 0.001), complications (r = 0.17, P < 0.001), life events (r = 0.13, P < 0.01), and diet (r = −0.09, P < 0.05).

Table 2 shows the cross-sectional relationships between each variable in the model and A1C at T1, with controls for all other variables. Patients who were nonwhite, had more comorbidities, had diabetes longer, and were receiving insulin had higher A1C at T1 than those who were white, had few comorbidities, had diabetes a shorter time, and were not receiving insulin. Of the three affective variables, however, a significant positive relationship with A1C was found only for DDS but not for MDD or CES-D. Not shown are models in which each of the three affective variables was entered into separate equations individually. Only DDS reached significance (P < 0.004); MDD and CES-D did not. The results were replicated in analyses with T2 and T3 cross-sectional data.

Prospective analyses
These analyses used T1 variables to predict change in A1C over time. Although the average change in A1C over time was not significantly different from zero for the sample as a whole, there was significant within-person variation in A1C change over time: slopes for 95% of the sample ranged from −0.122 to 0.128, with some decreasing and some increasing systematically over time. Table 2 shows that three T1 variables independently predicted change in A1C over time: older patients and those having diabetes longer displayed significantly greater decreases in A1C over time than younger patients and those with a more recent diagnosis of diabetes. Also, those with more comorbidities at T1 displayed greater increases in A1C over time than those with fewer comorbidities. None of the three affective variables significantly predicted change in A1C over time. Also,
Distress, depression, and glycemic control

Table 3—Time-covarying models predicting change in glycemic control over time (A1C)

<table>
<thead>
<tr>
<th>Model with three affective time-varying covariates</th>
<th>Complete model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient (b)</td>
<td>P</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Insulin ($1 = y e s ; 0 = n o$)</td>
<td>-0.026</td>
</tr>
<tr>
<td>BMI</td>
<td>0.006</td>
</tr>
<tr>
<td>No. complications</td>
<td>0.005</td>
</tr>
<tr>
<td>No. comorbidities</td>
<td>-0.001</td>
</tr>
<tr>
<td>No. stressful events</td>
<td>0.001</td>
</tr>
<tr>
<td>Diet</td>
<td>-0.002</td>
</tr>
<tr>
<td>Exercise</td>
<td>-0.002</td>
</tr>
<tr>
<td>MDD</td>
<td>-0.018</td>
</tr>
<tr>
<td>DDS</td>
<td>0.024</td>
</tr>
<tr>
<td>CES-D</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are unstandardized regression coefficients. Patient sex, race, age, education, and time since diagnosis also were included in the model.

none of the three reached significance when each was entered individually into separate regression models.

**Time-varying relationships**

These analyses added sets of time-varying covariates to the previous model to examine whether change in each characteristic was independently related to change in A1C over time. We included patient sex, ethnicity, age, education, and time with diabetes as covariates in these analyses but did not explore their time-varying relationships with A1C because these variables were viewed as being relatively fixed over time. These analyses provided statistical information only about the degree of time-concordant association between changes in a characteristic and changes in A1C over time; they did not provide information about the causal linkages between the two.

The first columns of Table 3 show the coefficients for the time-varying associations among the three affective variables and A1C, with all other variables entered as controls. Only DDS, but not MDD or CES-D, displayed a significant time concordant association with A1C ($b = 0.024, P = 0.001$). The right-hand columns of Table 3 show the independent time-varying relationships for all variables in the model. Again, only DDS displayed a significant time concordant relationship with A1C ($b = 0.023, P = 0.001$). When each of the affective variables was entered individually into separate models, only DDS reached significance ($P = 0.001$).

**CONCLUSIONS**— Ours is one of the few observational, noninterventional studies that explored both the cross-sectional and longitudinal relationships of MDD, depressive symptoms, and diabetes distress with glycemic control using well-established scales that specifically addressed each of the three affective constructs. With a comprehensive battery of controls in the models, we found no statistically significant cross-sectional, prospective, or time-concordant relationship between MDD and A1C or between depressive symptoms and A1C. Only distress specifically linked to diabetes displays both cross-sectional and time-varying longitudinal relationships with A1C. Distress, however, also shows no prospective relationship with A1C.

Congruent with prior research, we find no evidence of a statistically significant relationship between MDD and glycemic control or between depressive symptoms and glycemic control (8,21). A similar finding is provided by a recent study with both type 1 and type 2 diabetic patients that showed improvements in depressive symptoms after cognitive behavior therapy were not associated with changes in A1C (7). Thus, in both prospective studies, in which changes in MDD or in depressive symptoms occur after behavioral or pharmacological intervention, and in noninterventional studies, in which changes in symptoms or MDD are recorded over time, we see little or no concomitant changes in glycemic control. We conclude from these studies that the association between MDD and depressive symptoms with glycemic control is most likely modest at best and may be an artifact of the complex pattern of frequently uncontrolled interrelationships often found among a host of mood, diabetes status, treatment, behavioral, and life context variables.

These are illustrated by the T1 zero-order correlational findings reported above. If MDD and glycemic control are linked, it may be that depressive states have to of sufficient intensity and duration to demonstrate the effect, or it may be that there are multiple pathways between MDD and depressive symptoms with glycemic control and that they operate differently for different patients under different life contexts. If a causal link does exist, most likely there is no single, easily identified common pathway.

In contrast, we find that emotional distress specifically tied to diabetes and its management displays both cross-sectional and time-concordant relationships with A1C. These results do not necessarily imply a causative relationship between the two, especially because no significant prospective linkages between DDS and A1C were found. We suspect that each most likely influences the other over time, suggesting a bidirectional relationship (5) within the context of other co-occurring diabetes and life context variables (22). For example, for some patients, high disease distress can influence self-management and medication adherence with subsequent effects on glycemic control, and for other patients, poor control can lead to distress, which can influence disease management (23). This formulation of the relationship between diabetes distress and glycemic control does not assume the direct involvement of any physiological process but instead emphasizes the ongoing negative subjective experience of emotional distress around the management of a significant chronic condition that has implications for ongoing disease-related behavior, motivation, self-efficacy, and problem solving. Similar results have been reported with other chronic diseases as well (24,25).

It is also likely that some depressive symptoms partly reflect the negative emotional experience that surrounds disease-specific distress (26). This factor may explain the significant association between CES-D and DDS ($r = 0.48$), coupled with the finding that only DDS, but not CES-D, displays both independent cross-sectional and time concordant relationships with A1C. Thus, symptom inventories, such as CES-D, may tap into the negative emotional component of diabetes-specific distress.

In an effort to clarify and be more precise about what has been called depression in diabetes, it may be helpful...
clinically to consider and assess two relatively common conditions: MDD and diabetes-specific distress. For example, it has been shown that most individuals who are distressed about their chronic disease are not clinically depressed (27), that distress can be conceptually and empirically differentiated from depression and depressive symptoms, and that distress has stronger linkages with common psychological, behavioral, and social factors than clinical depression or depressive symptoms (26,28). Diabetes distress is about twice as prevalent as MDD in this population, is more persistent over time than MDD and high depressive symptoms, and is significantly and independently associated with a host of diabetes-related variables, e.g., BMI, complications, comorbidities, and self-management behaviors (26). Both MDD and diabetes distress are serious, treatable, and worthy of clinical concern.

There are several limitations to our findings. First, our use of a diverse community sample led to somewhat small subsamples of patients with defined affective conditions. Although we had sufficient statistical power to address the research questions posed, larger stratified samples might permit more comprehensive subgroup analyses. Second, we measured change across three assessments totaling 18 months. Studies with more frequent assessments that continue for a longer duration may yield additional findings. Third, the failure to observe a relationship between MDD and glycemic control may be partially due to a statistical issue: MDD is a dichotomous variable, whereas DDS, CES-D, and A1C are continuous variables, and correlations between continuous variables generally will be higher than correlations between a continuous variable and a binary variable. This is a problem inherent in a diagnostic approach and may argue for the use of more dimensional measures, which are generally more powerful. Fourth, some of the findings from the time-covarying analyses may have been influenced by patient knowledge of their A1C level.

In summary, we found no cross-sectional, prospective, or time-concordant associations between MDD and depressive symptoms with glycemic control, whereas significant cross-sectional and time-concordant relationships were found between diabetes distress and glycemic control. Given the linkages between diabetes distress and a host of diabetes management variables, we emphasize the importance of exploring further with empirical studies the interactive relationship between diabetes distress and glycemic control, screening for both MDD and disease-related distress in the clinical setting, and development of interventions for nondepressed but distressed patients with diabetes.

Acknowledgments — This research was supported by grants DK062732 and DK061937 from the National Institute of Diabetes and Digestive and Kidney Diseases. No potential conflicts of interest relevant to this article were reported.

APPENDIX — The following medical groups and diabetes education centers collaborated in this research: Alta Bates Diabetes Education Center, Brown and Tolland Medical Group, California Pacific Diabetes Education Center, Hill Physicians Medical Group, Marin IPA, St. Luke’s Diabetes Education Center, St. Mary’s Medical Center, and University of California, San Francisco Hospital and Clinics.

References
12. Tooher DJ, Hampson SE, Glasgow RE. The Summary of Diabetes Self-Care Activities measure: results from 7 studies and a revised scale. Diabetes Care 2000;23:943–950
14. Aikens JE, Wallander JL, Bell DS, Mc Norton A. A nomothetic-ideographic study of