

DIABETES DISTRESS AND NOT CLINICAL DEPRESSION OR DEPRESSIVE SYMPTOMS IS ASSOCIATED WITH GLYCEMIC CONTROL IN BOTH CROSS-SECTIONAL AND LONGITUDINAL ANALYSES

Running title: Distress, depression and glycemic control.

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Objective - To determine the concurrent, prospective and time concordant relationships between major depressive disorder (MDD), depressive symptoms (DS), and diabetes distress (DD) with glycemic control.

Research design and methods – In a non-interventional study, we assessed 506 type 2 patients for MDD (Composite International Diagnostic Interview), for DS (Center for Epidemiological Studies-Depression) and for DD (Diabetes Distress Scale), along with self-management, stress, demographics, and diabetes status, at baseline, 9 and 18 months later. Using multilevel modeling (MLM), we explored the cross-sectional relationships of the three affective variables with HbA1C; the prospective relationships of baseline variables with change in HbA1C over time; and the time-concordant relationships with HbA1C.

Results - All three affective variables were moderately inter-correlated, although the relationship between DS and DD was higher than either was with MDD. In the cross-sectional MLM, only DD and not MDD or DS was significantly associated with HbA1C. None of the three affective variables were linked with HbA1C in prospective analyses. Only DD displayed significant time-concordant relationships with HbA1C.

Conclusions – We found no concurrent or longitudinal association between MDD or DS with HbA1C, whereas both concurrent and time-concordant relationships were found between DD and HbA1C. What has been called “depression” among type 2 patients may really be two conditions – MDD and DD – with only the latter displaying significant associations with HbA1C. Ongoing evaluation of both DD and MDD may be helpful in clinical settings.

Clinical depression, depressive affect and diabetes distress are prevalent emotional states found among patients with diabetes (1). These states are associated with high morbidity and mortality (2, 3). One line of research has explored whether depression is a risk factor for diabetes or whether diabetes is a risk factor for depression. There are substantive data to suggest that depression is indeed a risk factor for subsequent depression (4) and that there may be a bidirectional relationship between depression and diabetes over time (5). A second line of research has explored the linkages between depression and glycemic control among patients already diagnosed with diabetes. Here the findings are less clear. In a landmark paper published in 2000, Lustman and colleagues presented a meta-analysis of the literature on depression and glucose control among patients already diagnosed with diabetes, and reported a modest but significant effect size ($d=.19$) (6). They raised several cautions about interpreting their results, however, because of concerns that some previous studies mixed type 1 and type 2 patients, used symptom measures that were not tied to defined diagnoses, were primarily cross-sectional, and lacked appropriate demographic and lifestyle controls. Subsequent studies of depression and glycemic control among patients already diagnosed with diabetes also have yielded mixed findings, and Georgiades, et al. recently listed 7 studies that demonstrated a significant relationship and 10 that did not (7). Furthermore, intervention trials to reduce depression among patients with diabetes have not consistently led to corresponding reductions in HbA1C or to improvements in self-care behavior (8, 9). And trials to improve diabetes self-care and glycemic control have not consistently led to a reduction in depression (10). Consequently, the causal linkages and pathways between

depression and glycemic control among patients already diagnosed with diabetes remain well studied but unclear.

Two major factors that contribute to this lack of clarity concern problems of definition and related measurement. Depression among patients with diabetes has been defined and measured in three ways in clinical research: (a) as a syndrome that meets DSM-IV criteria for major depressive disorder (MDD) usually assessed by a well-standardized, semi-structured interview (e.g., CIDI (11)); (b) as depressive symptoms assessed by general symptom inventories (e.g., BDI, CES-D (12, 13)) (counts of the number and/or severity of depressive symptoms as assessed by an instrument that documents mood states but does not link or associate each with particular events or life circumstances, like diabetes); and (c) as distress linked specifically to diabetes and its management assessed by diabetes-specific distress questionnaires (e.g., PAID (14), DDS (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 utilized 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 3-wave, longitudinal, observational study of 506 type 2 patients, we sought to clarify the differences and similarities among these three approaches to defining and measuring depression and their inter-relationships with glycemic control by examining the systematic co-variation 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 HbA1C (cross-sectional analysis)? Second, does the level or occurrence of any or all of these three at initial assessment significantly predict changes in HbA1C over subsequent study waves (prospective analysis). Third, do fluctuations in any or all of these three over study waves correspond with fluctuations in HbA1C over study waves (time-varying analysis)? In addition, we explored the impact of patient demographics, diabetes status, medications, self-management behaviors, and extra-disease 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: patient with type 2 diabetes; age 21-75 years; read and speak English or Spanish fluently; no severe diabetes complications (on dialysis, legally blind); and no diagnosis of dementia or psychosis. At initial assessment (T1) patients participated in a 1.5 hour 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 nine (T2) and 18 (T3) months later, at which time the same assessments were repeated. Mean between-wave interval was 9.1 months. Patients who met criteria for affective or anxiety disorder and who were

not being treated were referred to their physician. Approval was received by the IRB at UCSF and at each participating facility.

The dependent variable for all analyses was HbA1C. Patient demographics included gender, self-identified ethnicity (white/non-white), age, education (years), and time since diagnosis (years). Also collected were use of insulin (yes/no), BMI, number of complications and number of co-morbidities. Diet (DIET) and exercise (EXER) 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 they followed their DIET or EXER 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 Composite International Diagnostic Interview (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 Center for Epidemiological Studies-Depression Scale (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 Diabetes Distress Scale (DDS) (15), a continuous scale ($\alpha = .93$) that assesses each of 17 items across 6 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 between demographics, diabetes status, stress, self-management, the three affective variables, and baseline level and change in HbA1C 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 sub-group. 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 HbA1C. An unconditional means model partitioned the total variance of HbA1C 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 HbA1C over time and other changes in HbA1C not related to time. We then examined three analytic models. First, we evaluated how baseline predictors were related to baseline levels of HbA1C (cross-sectional analyses); and second, how these predictors were related to linear change in HbA1C 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 HbA1C over time. These models corresponded to the three research questions posed.

Time was centered at T1 and coded in years (0, .75, 1.5). The natural log of HbA1C 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 v9.2) using full maximum likelihood and robust standard errors (20). We also examined non-linearities among the continuous variables, and assessed a series of interactions among the three affective variables, as well as between each with age, gender, time with diabetes, and insulin use: all were non-significant. We also explored the impact of use of psychotropic medication in all models: again, all were non-significant. At each stage, residuals were examined for normality and heterogeneity.

RESULTS

Preliminary Analyses. Telephone screening identified 640 eligible individuals and 506 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.

About 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 to 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 ($r=.48$, $p<.001$) was notably higher than the relationship of these two variables with MDD (MDD with CES-D $r =.29$, $p<.001$; MDD with DDS $r =.15$, $p<.001$). Both CES-D ($r=.14$; $p=.002$) and DDS ($r=.17$; $p=.001$) were significantly correlated with HbA1C, whereas MDD was not ($r=-.05$). Of the 12

other variables in the multivariate model (Table 2), 8 displayed significant zero-order correlations with HbA1C: race/ethnicity $r = -.19$, $p < .001$; age $r = -.08$, $p < .05$; education $r = -.16$, $p < .001$; time with diabetes $r = .27$, $p < .001$; insulin use $r = .29$, $p < .001$; complications $r = .17$, $p < .001$; life events $r = .13$, $p < .01$; DIET $r = -.09$, $p < .05$).

Table 2 shows the cross-sectional relationships between each variable in the model and HbA1C at T1, controlling for all other variables. Patients who were non white, had more co-morbidities, had diabetes longer and were on insulin had higher HbA1C at T1 than those who were white, had few co-morbidities, had diabetes a shorter time, and were not on insulin. Of the three affective variables, however, a significant positive relationship with HbA1C was found only for DDS, 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 ($p < .004$); 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 HbA1C over time. Although the average change in HbA1C over time was not significantly different from zero for the sample as a whole, there was significant within-person variation in HbA1C change over time: slopes for 95% of the sample ranged from -0.122 to 0.128 , some decreasing and some increasing systematically over time. Table 2 shows that three T1 variables independently predicted change in HbA1C over time: older patients and those having diabetes longer displayed significantly greater decreases in HbA1C over time than younger patients and those with a more recent diagnosis of diabetes. Also, those with more-co-morbidities at T1 displayed greater increases in HbA1C over time than those with fewer co-morbidities. None of the three affective variables

significantly predicted change in HbA1C over time. Also, 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 HbA1C over time. We included patient gender, ethnicity, age, education, time with diabetes as covariates in these analyses but did not explore their time-varying relationships with HbA1C 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 HbA1C 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 between the three affective variables and HbA1C, with all other variables entered as controls. Only DDS displayed a significant time concordant association with HbA1C ($b = .024$, $p = .001$), not MDD or CES-D. 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 HbA1C ($b = .023$, $p = .001$). When each of the affective variables was entered individually into separate models, only DDS reached significance ($p = .001$).

CONCLUSIONS

Ours is one of the few observational, non-interventional 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 find no statistically significant cross-sectional, prospective or time concordant relationship between MDD and HbA1C or between depressive symptoms and HbA1C. Only distress specifically linked to diabetes displays both cross-sectional and time-varying longitudinal relationships with HbA1C. Distress, however, also shows no prospective relationship with HbA1C.

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 patients that showed that improvements in depressive symptoms following CBT were not associated with changes in HbA1C (7). Thus, in both prospective studies, in which changes in MDD or in depressive symptoms occur following behavioral or pharmacological intervention, and in non-interventional 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 inter-relationships often found among a host of mood, diabetes status, treatment, behavioral, and life context variables (22). 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 be 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 HbA1C. These results do not necessarily imply a causative relationship between the two, especially since no significant prospective linkages between DDS and HbA1C 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 may explain the significant association between CES-D and DDS ($r = .48$), coupled with the finding that only DDS, and not CES-D, displays both independent cross-sectional and time concordant relationships with HbA1C. Thus, symptom inventories, like 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, co-morbidities, 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 sub samples 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 sub group 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 HbA1C are continuous, and correlations between continuous variables generally will be higher than correlations between a continuous and a binary variable. This is a problem inherent in a diagnostic approach and may argue for using more dimensional measures, which are generally more powerful. Fourth, some of the

findings from the time co-varying analyses might have been influenced by patient knowledge of their A1C level. Future studies might explore the effects of this variable further. In contrast, the strengths of the study include a diverse community based sample with high rates of participation and retention, and the use of sophisticated data analytic procedures that permit maximum flexibility and power in analyzing both cross-sectional and longitudinal data.

In conclusion, we find 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 developing interventions for non depressed but distressed patients with diabetes.

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Table 1 – Sample description (N = 506)

Male/female subjects	218 (43%)/288 (57%)
Age (years)	57.8 +/- 9.8
Education (years)	14.7 +/- 3.3
Family income (\$1000)	52.8 +/-36.3
BMI (kg/m ²)	32.7 +/- 7.7
Psychotropic medications	105 (20.8%)
Number of co-morbidities	3.9 +/- 2.5
Number of complications	0.8 +/- 1.2
Years with diabetes	8.1 +/- 7.5
Insulin use	76 (15.0%)
Race/ethnicity	
Asian American	85 (16.8%)
African American	104 (20.4%)
Hispanic	99 (19.6%)
Non-Hispanic white	186 (36.8%)
Other	33 (6.5%)
HbA1C	7.2 +/- 1.44
DDS	2.1 +/- 1.0
CES-D	11.0 +/- 10.5
MDD	54 (10.7%)

Data are means +/- SD or n (%). DDS = Diabetes Distress Scale; CES-D = Center for Epidemiological Studies – Depression; MDD = major depressive disorder.

Table 2 – Cross sectional and prospective models predicting glyemic control (HbA1c)

	Cross-sectional model		Prospective model	
	Coefficient (b)	P	Coefficient (b)	P
Baseline/time	1.964	.01	.003	.56
Sex (1 = female; 0 = male)	-.004	.81	-.003	.78
Race (1 = white; 0 = non-white)	-.052	.001	-.001	.92
Age (years)	-.001	.36	-.001	.02
Education (years)	-.004	.08	-.001	.42
Time since diagnosis (years)	.005	.001	-.002	.03
Insulin (1 = yes; 0 = no)	.096	.001	-.001	.94
BMI	.001	.17	.001	.73
No. complications	.006	.30	-.005	.24
No. co-morbidities	-.007	.02	.004	.05
No. stressful events	.004	.07	.001	.80
DIET	-.006	.37	.004	.34
EXER	-.003	.36	.001	.63
MDD	-.027	.25	-.010	.55
DDS	.026	.006	-.005	.49
CES-D	-.001	.89	.001	.89
Residual covariance components				
Baseline			.019	.01
Time			.004	.01
Within-person			.007	.01
Covariance			-.001	.14

Data are unstandardized regression coefficients. Cross sectional model uses data from T1; prospective model uses T1 predictors of change in HbA1c over time.

EXER = exercise

Table 3 - Time co-varying models predicting change in glyemic control over time (HbA1c)

	Model with three affective time-varying covariates		Complete Model	
	Coefficient (b)	P	Coefficient (b)	P
Insulin (1 = yes; 0 = no)			-.026	.25
BMI			.006	.10
No. complications			.005	.41
No. co-morbidities			-.001	.62
No. stressful events			.001	.87
DIET			-.002	.69
EXER			-.002	.39
MDD	-.018	.17	-.017	.20
DDS	.024	.001	.023	.001
CES-D	.001	.151	.001	.18

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