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GLYCEMIC CONTROL AND MAJOR DEPRESSION IN PATIENTS WITH TYPE 1 AND TYPE 2 DIABETES MELLITUS

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Abstract—The current study evaluated the association of glyceemic control and major depression in 33 type 1 and 39 type 2 diabetes mellitus patients. Type 1 patients with a lifetime history of major depression showed significantly worse glyceemic control than patients without a history of psychiatric illness ($t=2.09$; $df=31$, $p<0.05$). Type 2 diabetes patients with a lifetime history of major depression did not have significantly worse control than those with no history of psychiatric illness. Findings from this study indicate different relationships between lifetime major depression and glyceemic control for patients with type 1 and type 2 diabetes. Treatment implications for glyceemic control in type 1 and type 2 diabetes patients are discussed. © 1999 Elsevier Science Inc.

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INTRODUCTION

Depressive disorders have been found to occur at increased prevalence rates among patients with type 1 (formerly known as juvenile-onset) and type 2 (formerly known as adult-onset) diabetes mellitus. Lifetime prevalence rates of major depression among type 1 and type 2 diabetes patients range between 14.4% and 32.5% [1–11]. Despite variation in the degree of prevalence in this population, these studies suggest that a sizable proportion of patients with diabetes show evidence of clinically meaningful depressive disorders.

A few studies have explored the relationship between depression and key medical variables in diabetes. One such critical indicator is glyceemic control. Prolonged poor glyceemic control has been demonstrated to result in more rapid onset and progression of retinopathy, neuropathy, and nephropathy [12–16], which have been linked with decreases in quality of life [12, 17, 18] and increased mortality [19]. Studies documenting the impact of depression on glyceemic control have varied in the methods of assessment, from self-reported questionnaire data [20–22] to standardized

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psychiatric interview protocols [2, 4, 23]. Although self-report questionnaires provide symptom endorsement, they do not allow clinical evaluation of the degree to which symptoms are organized into episodes, impair functioning, or represent somatic manifestations of diabetes-related complications unrelated to mood syndromes.

Three principal studies have utilized psychiatric interviews for the diagnosis of major depression [2, 4, 23]. Lustman and colleagues [2] found, in a mixed group of type 1 and type 2 patients, those with a diagnosis of major depression within 12 months of diagnostic interview had significantly worse glycemic control (HbA1) than patients with no history of any psychiatric illness. Psychiatric illness was evaluated using the Diagnostic Interview Schedule (DIS) by clinical interviewers who were blind to glycemic status.

Robinson and colleagues [4] studied a combined sample of type 1 and type 2 adults to examine the prevalence of depression and presence of complications in four groups of diabetes patients compared with controls: normals; depression cases; subthreshold or borderline depression cases; and past history or recovered cases. A modified version of the Present State Exam (PSE) was used to assess psychiatric illness. The investigators did not find significant differences in current glycemic control, as indexed by HbA1, among normal controls and patients who were currently depressed cases, borderline depression, or patients who had a past history of depression. Significant differences in mean postprandial blood glucose values were found. Patients with borderline depression reported the highest blood glucose values. Patients with a past history of depression reported the lowest mean blood glucose values.

Finally, in an investigation of the relationship between lifetime history of psychiatric illness and the severity of early retinopathy, Cohen *et al.* [23] compared HbA1 values among three type 1 samples: those with a history of any psychiatric illness; those with a lifetime history of affective illness; and those with a lifetime history of major depression. Cohen's group found significantly worse glycemic control in the affective illness and any psychiatric history samples when compared to a psychiatric-illness-free reference sample. The small subgroup of patients with a lifetime history of major depression showed elevated glycemic levels compared to the reference sample, but the difference did not meet statistical significance.

Variable findings from these studies may be attributable to differing samples. Lustman *et al.* [2] and Robinson *et al.* [4] used combined type 1 and type 2 samples to conduct their analyses, whereas Cohen *et al.* [23] selected a type 1 sample with limited disease duration (8 to 15 years) in order to examine the effect of psychiatric illness history and the development of diabetic retinopathy. The combination of type 1 and type 2 patients into a single sample poses challenges to understanding a relationship of glycemic control to depression. Type 1 and type 2 diabetes are distinct diseases with differing etiologies, ages of onset, risk factors, and treatment regimens. Among patients with type 2 diabetes, patients vary considerably in their prescribed treatment regimens; that is, diet only, oral agents, and/or insulin injections. Given these differences, the relationship between glycemic control and depression may differ significantly between diabetes types and across diabetes treatment regimens. Neither Robinson [4] nor Lustman [2] conducted separate analyses by diabetes type. Thus, it is not yet known whether the relationship of depression to glycemic control differs in type 1 and type 2 diabetic patients.

The timeframe for the diagnosis of major depression episodes also differed across these studies. Lustman and colleagues reported significant findings for patients with a recent history of major depression, but did not report results for patients with a lifetime history of major depression. In the studies that examined lifetime history of major depression, Cohen et al. [23] reported a nonsignificant trend toward worsened glycemic control, whereas Robinson et al. [4] reported worsened postprandial blood glucose levels for patients with a past history of depressive illness. The correspondence of time and glycemic control is a potentially important indicator of an underlying mechanism that might be responsible for a relationship between psychiatric history and glycemic control. An enduring effect of past episodes of major depression on glycemic functioning would have important consequences for the development of long-term diabetes complications such as retinopathy, neuropathy, and nephropathy. Further exploration of a possible long-term effects is necessary to clarify this point.

This study was proposed to examine the relationship of glycemic control to both current and lifetime major depression in a cohort of adult patients with type 1 and type 2 diabetes. Specifically, we hypothesized that: (1) type 1 patients with *current* major depression would show worse glycemic control than type 1 patients with no history of psychiatric illness; (2) type 2 patients with *current* major depression would show worse glycemic control than type 2 patients with no history of psychiatric illness; (3) type 1 patients with a *lifetime* history of major depression would show worse glycemic control than type 1 patients with no history of psychiatric illness; and (4) type 2 patients with a *lifetime* history of major depression would show worse glycemic control than type 2 patients with no history of psychiatric illness.

RESEARCH DESIGN AND METHODS

Sample and procedures

Thirty-three type 1 and 39 type 2 diabetes patients were selected for analyses from a larger investigation of psychiatric prevalence in an out-patient diabetic sample. Sample selection criteria for the purposes of the current investigation follow a brief description of the original sample recruitment procedures. In the initial data pool, 240 type 1 and type 2 subjects were recruited during consecutive visits to internal medicine appointments to the Joslin Diabetes Center. After signing a written informed consent, subjects completed a screening questionnaire on psychiatric symptoms during the preceding 1-month period (SCL-90R [24]). Further psychiatric evaluation using the Structured Clinical Interview for the DSM-III-R (SCID [25, 26]) was conducted with patients meeting "caseness" (N=75; caseness defined by Derogatis and colleagues [24] as a *t*-score of ≥ 63 on the Global Severity Index) and an additional 40% of randomly selected patients (N=68) who scored below the caseness threshold. A total of 143 subjects with type 1 and type 2 diabetes were interviewed. Sample recruitment for the larger sample is discussed elsewhere [27].

From the 143 subjects who received SCID interviews, subjects were selected for the current analyses using the following criteria: presence of glycosylated hemoglobin data collected at the time of study enrollment; classification of diabetes type; and SCID diagnosis in one of two categories: (1) lifetime history of major depression; or (2) absence of any psychiatric illness history. Of the type 1 and type 2 subjects who received a SCID interview, 19 subjects with type 1 diabetes met SCID diagnostic criteria for a lifetime history of major depression and 14 type 1 subjects with negative psychiatric histories met inclusion criteria. Of the type 2 subjects who received a SCID interview, ten subjects met criteria for a lifetime history of major depression, whereas 29 subjects had no history of psychiatric illness and had glycosylated hemoglobin values. Procedures for assessment of inclusion criteria are discussed in what follows.

Diagnostic assessment

Diabetes type. Diabetes type was assigned according to the established diagnostic criteria used by diabetologists in the Joslin Diabetes Clinic. Diabetes type was gathered from each patient's primary diabe-

tologist and a review of medical charts 1 month prior to study intake by a research assistant who was blind to the glycemic status of patients.

Psychiatric diagnoses. Patients contacted for psychiatric evaluation were assessed for lifetime and 6-month histories of psychopathology using the Structural Clinical Interview for DSM-III-R [25, 26]. Interviews began with an open-ended overview where occupational, social, psychiatric, and medical history was obtained on a timeline. Diabetes onset and course was recorded during this segment of the interview. In each diagnostic module, psychiatric symptoms were rated as absent, subthreshold, or present and evaluated for psychiatric etiology. The hierarchy of diagnoses within Axis I disorders adopted by the DSM-III-R was used in assigning diagnoses. The SCID has been demonstrated to have good test-retest reliability in patient samples [26]. SCID interviews were conducted by a master's level clinical interviewer (M.d.G.) who was trained to reliability at the Depression Research Facility at McLean Hospital. Interrater reliability in training this interviewer was established against "gold-standard" interview ratings of patient interviews at McLean Hospital (criterion=intraclass correlation>0.60). Case histories and diagnoses were reviewed and assigned during case conferences attended by three investigators comprising the research team (A.M.J., J.A.S., and M.d.G.) who were blind to glycemic status.

Glycemic control. Glycosylated hemoglobin values (HbA1) prepared using the agar gel electrophoresis process ([28] normal range for nondiabetic samples 5.4% to 7.4%) were recorded from patient medical records for the date closest to study intake (in most cases on the same day) in a review of medical records approximately 1 year following psychiatric interview. Glycosylated hemoglobin is reported as a percentage of total hemoglobin and is used to estimate the average blood glucose control over the 2-month period prior to measurement.

Data analyses

For each sample, Student's *t*-test was used to test mean differences between psychiatric diagnostic groups for HbA1, number of complications, and duration of diabetes. Chi-square analyses were conducted to compare psychiatric diagnostic group and gender, marital status, and education. A 2×2 factorial analysis of variance was conducted to compare the means of HbA1 by psychiatric group and diabetes type.

In addition to significance tests, effect size was calculated to estimate the strength or magnitude of association of between-group comparisons. Using Cohen's [32] guidelines for effect sizes in the behavioral and social sciences, a small effect size measured by Cohen's *d* would equal 0.20, a medium effect size 0.50, and a large effect size would equal 0.80 or greater.

RESULTS

Demographic characteristics for subjects with a lifetime history of major depression and those with no psychiatric illness for type 1 and type 2 patients are provided in Table I. Lifetime major depression groups did not differ from the reference groups (no history of psychiatric illness) in terms of marital status, education, or duration of diabetes in either type 1 or type 2 samples. Among type 2 patients, those with a lifetime history of major depression were younger than those in the psychiatrically well group ($t=2.35$, $df=37$, $p<0.03$).

Student's *t*-test was performed to compare the mean HbA1 values for patients with a lifetime history of major depression and patients with no psychiatric illness. Type 1 patients with a lifetime history of major depression showed significantly higher mean HbA1 values ($t=2.09$; $df=31$, $p<0.05$) than the type 1 reference group. Type 2 patients with a lifetime history of major depression failed to show significantly different HbA1 values than the type 2 reference group ($t=1.92$, $df=37$, $p<0.06$). Results are shown in Table II.

A 2×2 factorial ANOVA was conducted for psychiatric illness group (e.g., lifetime major depression vs. no psychiatric history) by diabetes type to determine whether there were statistically significant differences in the mean glycemic control values between type 1 and type 2 diabetes samples. A significant interaction effect was found [$F(1, 71)=8.63$, $p<0.005$] indicating that glycemic control mean values in the nonpsychiatric and lifetime major depression groups varied as a function of diabetes type.

Table I.—Social demographic characteristics of patients with a lifetime history of major depression and patients with no history of psychiatric disorder by diabetes type

	No lifetime psychiatric history	Lifetime history of major depression
Type 1 subjects	(N = 14)	(N = 19)
Age (in years)		
Mean (sd)	50.3 (19.8)	39.4 (12.5)
Gender		
Male	8 (57.1%)	10 (52.6%)
Female	6 (42.9%)	9 (47.4%)
Education		
Less than high school	2 (14.3%)	1 (5.3%)
High school or greater	12 (85.7%)	18 (94.7%)
Marital status		
Never married	2 (14.3%)	5 (26.3%)
Married	11 (78.6%)	9 (47.4%)
Separated/divorced	1 (7.1%)	5 (26.3%)
Duration of diabetes (in years)		
Mean (sd)	22.3 (11.6)	22.6 (12.5)
Type 2 subjects	(N = 29)	(N = 10)
Age (in years)		
Mean (sd)	62.4 (10.7)	53.3 (10.6) ^a
Gender		
Male	16 (55.2%)	6 (60%)
Female	13 (44.8%)	4 (40%)
Education		
Less than high school	4 (13.8%)	—
High school or greater	25 (86.2%)	10 (100%)
Marital status		
Never married	3 (9.7%)	—
Married	21 (72.4%)	9 (90%)
Separated/divorced	5 (17.9%)	1 (10%)
Duration of diabetes (in years)		
Mean (sd)	12.7 (7.8)	9.5 (4.9)

^a No psychiatric history vs. lifetime major depression in type 2 sample: $t = 2.35$; $df = 37$; $p < 0.03$.

To test whether our data would replicate the results of Lustman et al. [2], a Student's t -test was performed to compare mean glycosylated hemoglobin values for the no psychiatric illness group and a subset of patients who reported an episode of major depression within 6 months prior to interview. Although our data suggest that mean HbA1 values of recent major depression were elevated compared to the no psychiatric illness group in type 1 patients, we did not find a statistically significant difference ($t=1.98$, $df=17$, $p<0.09$) in type 1 patients. Type 2 patients with a history of recent major depression also showed no significant differences in their glycemic control compared to the reference group ($t=1.94$, $df = 31$, $p<0.06$).

DISCUSSION

When type 1 and type 2 diabetes patients were studied separately, our findings indicated that the relationship of glycemic control to major depression differed by diabetes type. Type 1 patients with a lifetime history of major depression had

Table II.—Mean glycosylated hemoglobin values of no lifetime psychiatric history and lifetime history of major depression by diabetes type

	HbA1 values, mean (sd)	
	No Lifetime psychiatric history	Lifetime history of major depression
Type 1	10.4 (1.6)	11.7 (2.0) ^a
Type 2	11.1 (2.1)	9.6 (1.9)

^a Student's *t*-test for no history of psychiatric illness vs. lifetime major depression: $t = 2.09$; $df = 32$; $p < 0.05$.

poorer glycemic control than patients with no history of psychiatric illness. Type 2 patients showed consistent glycemic control levels regardless of depression history status. The significant interaction found in the factorial ANOVA underscores the importance of separating analyses by diabetes type when comparing glycemic control in subjects with a lifetime history of major depression to subjects with no psychiatric history.

Differences found according to diabetes type in our sample may be due to a variety of inherent differences between type 1 and type 2 diabetes, including type of treatment, the impact of the disease on physical and psychological functioning, and the quality of life resulting from the disease. Type of treatment, for example, may play an important distinguishing characteristic within type 2 patient samples. Type 2 patients who are treated with diet only or oral agents continue to produce endogenous insulin, which may reduce the behavioral and hormonal impact of depression on glycemic control. It is possible that type 2 patients who are treated with insulin injections might demonstrate similar glycemic control sensitivity to type 1 patients in the presence of a lifetime history of major depression. Further investigation is necessary to clarify whether type of treatment may be an important mediating factor in the relationship of major depression to glycemic control in type 2 patients.

Consistent with the findings from previous articles, we found a statistically significant relationship between glycemic control and a *lifetime* history of major depression in type 1 patients and a nonsignificant trend in poorer glycemic control in a subsample of type 1 patients where the onset of major depression was within 6 months of the diagnostic interview. Although we did not find a significant relationship between glycemic control and recent major depression, this discrepancy in our results, compared to the work of Lustman and colleagues, is most likely due to small sample size in our recent major depression group ($n=5$). Inspection of the mean values shows that our findings replicate the trend, if not the results, of Lustman's work. Inspection of effect sizes that were calculated for each significant *t*-test comparison showed a medium effect size for type 1 patients with and without a lifetime history of major depression (Cohen's $d=0.70$). This effect size is comparable to those of Lustman and colleagues [2] (Cohen's $d=1.03$, large effect), Robinson and colleagues [4] (Cohen's $d=0.64$, medium effect) and Cohen and colleagues [23] (Cohen's $d=0.58$, medium effect).

The sample size of the current study places limitations on the generalizability of study findings. Larger sample sizes, which enable comparisons across diabetes types

and various treatments, are necessary to investigate the role of glycemic control and changes in behavioral self-care that are attributable to depression. Likewise, samples drawn from multiple diabetes treatment sites would further enhance the generalizability of study findings. In the current study, the sample was drawn from a single source.

Both physiologic and behavioral mechanisms have been hypothesized to underlie the relationship between depression and glycemic control in diabetes. Hormonal and neurological hypotheses include: changes in the pituitary–adrenal cortical system through the effect of cortisol [30, 31]; changes from the effect of epinephrine and norepinephrine on the sympathetic–adrenal medullary system [30, 31]; changes due to increased glucagon secretion [30]; and elevated growth hormone levels in response to emotional stressors [32].

Another physiological component in the relationship between glycemic control and lifetime major depression is the extent to which pharmacologic treatment of depression impacts glycemic control. Monoamine oxidase inhibitors [33] and serotonin-reuptake inhibitors [33–36] have been shown to decrease blood glucose levels in laboratory and human investigations, whereas tricyclic antidepressants have been noted to increase serum blood glucose [33, 37]. Future studies of the relationship of depression and blood glucose levels in diabetes patients should address pharmacologic treatment histories for patients with lifetime and recent histories of major depression for type 1 and type 2 patients separately.

However, it is likely that behavioral mechanisms play the largest role in the relationship between depression and glycemic control. Indeed, adherence to diabetes regimen has been assumed to be the critical contributor to glycemic control. Diabetes requires adhering to a complex set of treatment regimens including medication administration, monitoring blood glucose values, adherence to specific or general dietary guidelines, routine exercise, as well as routine foot inspection and care and attending regular medical exams. These self-care behaviors have been considered to be a significant component of health outcomes [38]. Surprisingly, studies examining adherence as a predictor of glycemic control (as one health outcome) have shown inconsistent results [39, 40]. Inconsistency in research findings in regard to the relationship between adherence and glycemic control may be a function of the complexity of adherence as a construct. Aspects of this complexity include: differences in the definition of adherence across studies; qualitative differences in the types of prescribed behaviors to which patients must adhere (e.g., diet vs. exercise vs. medication adherence); imprecise methodology used to measure adherence; degree of specificity to behavioral prescriptions communicated by health professionals; and physiological factors beyond the control of patients [38, 41].

Several studies have examined the relative correlation of depressed mood to glycemic control compared to the contribution of other psychosocial factors such as adherence to prescribed regimen, coping strategies, and perception of control over diabetes to glycemic control. Using structural equation modeling, Daviss et al. [42] found that total competence, dietary adherence, and frequency of blood glucose testing more strongly predicted glycemic control than depressive symptoms on the Child Behavior Checklist in type 1 youths. Eaton et al. [43] found depression to show comparable correlations with blood glucose control compared to family cohesiveness and behavioral adherence in a sample of 127 predominantly adult type 1

patients. Using path analysis, Lustman *et al.* [37] examined the relative contribution of nortriptyline and improvement in depression on glycemic control in a sample of 68 type 1 and type 2 diabetes patients. While nortriptyline showed negative effects (hyperglycemic) on blood glucose levels, reduction in depressive symptoms had a positive effect (hypoglycemic) on blood glucose levels. Adherence with diabetes regimen was hypothesized by the authors to account for the relationship between depressive symptoms and HbA1c although small sample sizes prevented empirical validation of this hypothesis. Further work is needed to document the role these factors may play in type 1 and type 2 patients separately.

The direction of the relationship between depression, behavior, and glycemic control remains unclear. Depression may be the precipitant of poor glycemic control or the result of failed efforts to improve blood glucose control. A cycle of effects may occur where feelings of disappointment about poor glycemic control may affect adherence to one's prescribed regimen, in turn worsening glycemic control. Longitudinal studies that track the course of disease, psychiatric comorbidity, and glycemic control at multiple points in time are needed to distinguish the trajectory of impacts among these variables. All but one study examining the relationship between depression and glycemic control, to date, have been cross-sectional designs [2, 4, 23]. Lustman *et al.* [44] recently reported 5-year follow-up data for patients undergoing a randomized clinical trial of antidepressant treatment. Although these data documented worsened glycemic control in patients with recurrent major depression compared to baseline, comparison of glycemic status for nondepressed controls at baseline and follow-up was not presented. Measures of adherence to a prescribed regimen during the follow-up period were not reported, thus leaving open the question of the direction of impacts on glycemic control.

If depression is assumed to affect glycemic control, there are several possible mechanisms for an enduring impact of a lifetime history of depression on glycemic control including: (1) neuropsychological impacts of depression on memory and diabetes self-care knowledge; (2) persistent subthreshold depression affecting adherence; and (3) negative diabetes attitudes affecting self-care. Depression could also serve as a "marker" for the presence of other attitudinal or personality variables such as low self-esteem or personality disorder that are present throughout the patient's diabetes history [45]. Because depression includes symptoms of pessimism, poor concentration, and loss of interest, it is reasonable to assume that both learning and adherence are affected in patients with depression.

The results from the current study point to an association between glycemic control and lifetime history of major depression in patients with type 1 diabetes. With this relationship in mind, the presence of high HbA1 values may be a useful marker for the clinician. In addition to investigating blood glucose self-monitoring, exercise, diet, and insulin regimens, the health care provider can screen for current and lifetime history of depressive symptomatology. Early identification of depression has been demonstrated in general practice populations to reduce episode duration in anxiety disorders and to increase mental health interventions [46]. Likewise, studies of the effect of psychiatric status on medically ill patients have found that persistent affective disorder was associated with continuing physical illness [47], increased use of health services [48], and increased risk of mortality in patients with myocardial infarction [49, 50]. Taken together, psychiatric illness may place the patient with

type 1 at greater risk for persistently poor blood glucose control, thereby contributing to the progression of complications and early mortality. Recognition of the association of lifetime and current depression with high HbA1 values may be useful to guide clinicians toward more aggressive treatment of the underlying psychiatric conditions in order to affect diabetes self-care (self-monitoring, changes to diet, exercise, and insulin regimen).

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