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Mental health symptoms and patient-reported diabetes symptom burden: implications for medication regimen changes

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Abstract

Aims. To examine the relative contribution of glycaemic control (HbA1C) and depressive symptoms on diabetes-related symptom burden (hypoglycaemia and hyperglycaemia) in order to guide medication modification.

Methods. Secondary analysis of medical records data and questionnaires collected from a racially/ethnically diverse sample of adult patients with type 2 diabetes ($n = 710$) from seven outpatient clinics affiliated with an academic medical centre over a 1-year period as part of the Reducing Racial Disparities in Diabetes: Coached Care (R2D2C2) study.

Results. Results from linear regression analysis revealed that patients with high levels of depressive symptoms had more diabetes-related symptom burden (both hypoglycaemia and hyperglycaemia) than patients with low levels of depressive symptoms ($\beta s = 0.09$–0.17, $Ps < 0.02$). Furthermore, results from two logistic regression analyses suggested that the odds of regimen intensification at 1-year follow-up was marginally associated with patient-reported symptoms of hypoglycaemia [adjusted odds ratio (aOR) = 1.24, 95% CI: 0.98–1.58; $P = 0.08$] and hyperglycaemia (aOR = 1.21, 95% CI: 1.00–1.46; $P = 0.05$), after controlling for patients' HbA1C, comorbidity, insulin use and demographics. These associations, however, were diminished for patients with high self-reported hypoglycaemia and high levels of depressive symptoms, but not low depressive symptoms (interaction terms for hypoglycaemia by depressive symptoms, aOR = 0.98, 95% CI: 0.97–0.99; $P = 0.03$).

Conclusions. Mental health symptoms are associated with higher levels of patient-reported of diabetes-related symptoms, but the association between diabetes-related symptoms and subsequent regimen modifications is diminished in patients with greater depressive symptoms. Clinicians should focus attention on identifying and treating patients' mental health concerns in order to address the role of diabetes-related symptom burden in guiding physician medication prescribing behaviour.

Key words: Diabetes-related symptom burden, mental health, physician medication prescribing behaviour, type 2 diabetes.

Introduction

Comorbid depression has been observed in over 20% of patients with diabetes—almost double the prevalence observed in the non-diabetic population (1). While some cross-sectional studies that

have primarily focused on non-Hispanic white patients suggest that depression is significantly associated with increased self-reported hypoglycaemia and hyperglycaemia in type 2 diabetes patients (2), other studies have found that this association was not significant

(3). Furthermore, depression has been found to be associated with non-specific symptom amplification in patients with chronic medical illness (4), which suggests an increased potential for diabetes-related symptom reporting among diabetic patients who are also depressed. In Asian and Latino cultures, in particular, mental health problems often are manifested as somatic symptoms (5,6). Thus, racially/ethnically diverse diabetic patients with depression may have a lower threshold for reporting physical symptoms, including common diabetes symptoms. Because physicians make treatment decisions based, in part, on patient symptoms, this tendency among some depressed patients to report greater diabetes-related symptoms may influence the prescribing habits of providers. Thus there is a need for research that examines the extent to which a self-rated outcome, such as diabetes-related symptom reporting, is associated with patients' psychological status, and in turn, with physician prescribing behaviour.

Given the adverse effect of depression on diabetes-related symptoms and associated complications (3,7), treating patients' depressive symptoms may lead to a more accurate assessment of symptom burden, and therefore, better guidance for treatment. Although there is support for the effectiveness of treating depressive symptoms in patients with diabetes (8,9), little is known about how the somatic manifestations of mental health issues are associated with diabetes-related symptoms among racially/ethnically diverse samples of patients with type 2 diabetes. In this study, we hypothesized that in addition to actual glycaemic control, patients' mental health symptoms would be associated with their reports of diabetes-related symptom burden (i.e. hypoglycaemic and hyperglycaemic symptoms). We also sought to examine whether patient-reported diabetes-related symptom burden was associated with physicians' prescribing behaviours above and beyond a clinical indicator of glycaemic control (i.e. patients' haemoglobin A1C; HbA1C).

Patients and methods

Research design
Cross-sectional data were collected at seven university-affiliated primary care clinics in Southern California. Patients were excluded if they were age <18 or ≥80, had a diagnosis of schizophrenia, or could not speak English, Spanish or Vietnamese. Of the eligible patients approached (N = 1971), 75.3% provided written informed consent to complete a baseline questionnaire and allowed access to their medical record information, laboratory and administrative data. A subset of patients with HbA1c >7.5% were followed longitudinally, and comprise the analytic sample for this secondary analysis (N = 710). Medical records were abstracted for the 12-month period leading up to the date the questionnaire was completed (baseline), and for the 12-month period following the baseline date (year 1). The research design and all study procedures were approved by the University of California, Irvine's Institutional Review Board.

Measures
Glycaemic control
Patients' HbA1C levels were measured by the central laboratory at the University of California Irvine Medical Center using the D-10 Hemoglobin Testing System (Bio-Rad Laboratories, Hercules, CA), and were abstracted from patients' medical records for the year prior to the start of the study through the entire study period.

Patient-reported diabetes-related symptom burden
Symptoms of glucose dysregulation were assessed in the baseline questionnaire by asking patients how often they experienced diabetes-related symptoms in the following areas: hypoglycaemia and hyperglycaemia. Hyperglycaemia was assessed by asking respondents how often they experienced symptoms of high blood sugar (e.g. thirst or frequent urination). Ratings were made on a five-point scale (1 = never, 5 = every week or more). Hypoglycaemia was assessed by asking patients how often they experienced symptoms of low blood sugar episodes (e.g., sweating, weakness, trembling, shakiness, or an 'insulin reaction'). Ratings were made on a five-point scale (1 = never, 5 = every week or more). These two items were originally developed as part of the Patient Outcome Research Team (PORT) study, a longitudinal observational study of patients with type 2 diabetes (10). Single item ratings of perceived frequency of hypoglycaemia and hyperglycaemia, such as the ones used in this study, have been shown to be associated with low health-related quality of life (11) and increased mortality risk (12).

Mental health symptoms
A 10-item version of the Center for Epidemiological Studies Depression (CES-D) scale (13) was used to assess severity of depressive symptoms. Items that are typically used to assess somatic symptoms associated with depressive symptomatology, and that might overlap with diabetes-related symptom burden, were removed from the scale (e.g. sleep was restless, appetite was poor). This abbreviated version, adapted from the full 20-item CES-D, has been validated against other psychiatric measures of depression in ethnically diverse samples (5), and exhibited good internal consistency for each racial/ethnic group (Cronbach's α ranged between 0.90 and 0.92). Scores on the abbreviated measure were rescaled to have the same range of values as the full measure. A cut-off score of ≥22, which has been shown to have good sensitivity and specificity for screening for major depressive disorder among chronically ill patients (14), was used to indicate clinically relevant levels of depressive symptoms.

Physician medication prescribing behaviours
To determine if providers had changed patients' diabetes-related medications (e.g. glucose lowering medications) in the 12 months following the baseline questionnaire, participants' medical charts were examined using a structured chart abstraction form to record all medications noted as either being currently taken by the patient or prescribed by a provider, and the presence of any changes in medication in patients' medical records (including in the problem list, chart notes or in referrals). We coded for eight classes of medications prescribed to treat hyperglycaemia [i.e. biguanides, sulfonylureas, thiazolidinediones (TZDs), DPP-4 inhibitors, α-glucosidase inhibitors, meglitinides, GLP-1 agonists and insulin] (15). A binary summary score was retained for analysis for each person as positive based on any intensification of the patient's diabetes medication, including an increase in dose, a change in class of diabetes-related medication, or initiation of a new diabetes medication.

Covariates
Burden from comorbid illness was measured using a 59-item version of the Total Illness Burden Index (TIBI) (16), a summary measure of the presence and severity of the patient's diseases and symptoms that has been previously modified to reflect different index conditions. TIBI scores ranged from 0 to 16. Other covariates included standard demographic characteristics, such as race/ethnicity (non-Hispanic white, Mexican American, Vietnamese American), sex (female, male), age and education (less than a high school education, at least a high school education). All covariates were assessed as part of the baseline questionnaire.

Data analysis

The data analysis was completed in three phases. First, we compared the demographic and clinical characteristics of the patients with high versus low depressive symptoms using independent samples *t*-tests (for continuous variables) and χ^2 tests (for categorical variables). We then conducted two hierarchical ordinary least-squares regressions to examine the independent and additive main effects of HbA1C and depressive symptoms on diabetes-related symptom burden. Specifically, the independent main effect of HbA1C was examined as a predictor of diabetes-related symptom burden, adjusting for all covariates in step 1 of the model; depressive symptoms was added as predictor of diabetes-related symptom burden in step 2 of the model, adjusting for all covariates in the model. Finally, the differential associations between diabetes-related symptom burden and subsequent physician prescribing behaviours (the addition of a new diabetes-related medication in the following year) for patients with varying levels of depressive symptoms (high versus low scores on the CES-D) were examined using logistic regression models including a depressive symptom by diabetes-related symptom burden interaction term. Models were adjusted for standard demographic characteristics, including race/ethnicity, gender, age and education. All analyses were performed using SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY), and two-tailed *P* values less than or equal to 0.05 were considered to be statistically significant.

Role of the funding source

The study was funded by the National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). The funding agency had no role in the design, conduct or analysis of the study or in the decision to submit the manuscript for publication.

Results

Table 1 compares the demographic and health characteristics of the sample for patients with low versus high depressive symptoms. In general, there were very few significant demographic or health status differences between these two groups. However, patients with high depressive symptoms generally had greater burden from comorbid illness (3.3 versus 5.6, *P* < 0.001). Finally, patients with higher depressive symptoms reported more frequent hypoglycaemia (2.8 versus 1.9, *P* < 0.001) and hyperglycaemia (3.4 versus 2.7, *P* < 0.001) compared to patients with low depressive symptoms.

As shown in Table 2 (left side), results from a hierarchical linear regression analysis that adjusted for patients' sociodemographic characteristics revealed that HbA1C was inversely associated with patient-reported hypoglycaemic symptoms (β = –0.11, *P* = 0.01). Insulin use (β = 0.14, *P* < 0.001), burden from comorbid illness (β = 0.23, *P* < 0.001) and depressive symptoms (β = 0.17, *P* < 0.001) were positively associated with patient-reported hypoglycaemic symptoms. As shown on the right side of Table 2, insulin use (β = 0.10, *P* = 0.01), HbA1C (β = 0.11, *P* = 0.008) burden from comorbid illness (β = 0.29, *P* < 0.001) and depressive symptoms (β = 0.09, *P* = 0.02) were each positively associated with hyperglycaemic symptoms.

Logistic regression models revealed that the association between patient-reported hypoglycaemia and physician prescribing behaviours varied as a function of the patient's level of depressive symptoms (see Table 3, Model 1). Overall, there was a trend suggesting a marginal association between patient-reported hypoglycaemia and subsequent regimen intensification [adjusted odds ratio (aOR) = 1.24, 95% CI: 0.98–1.58; *P* =0.08) and a significant association between depressive symptoms and regimen intensification (aOR = 1.03, 95% CI: 1.00–1.05; *P* = 0.01). Further more, there was a significant interaction between patient-reported hypoglycaemia and depressive symptoms (aOR = 0.98, 95% CI: 0.97–0.99; *P* = 0.03), suggesting the association between hypoglycaemia and regimen intensification was diminished with every unit increase in depressive symptoms.

A similar pattern was observed for patient reported hyperglycaemia (Table 3, Model 2). There was a trend suggesting a marginal association between patient-reported hyperglycaemia and regimen intensification in the next year (aOR = 1.21, 95% CI: 1.00–1.46; *P* = 0.05), and a significant association between depressive symptoms and regimen intensification (aOR = 1.03, 95% CI: 1.01–1.05; *P* = 0.04). The interaction between hyperglycaemia and depressive symptoms was not significant (aOR=0.99, 95% CI: 0.98–1.00; *P* = 0.09).

Discussion

The findings from this study suggest that both patients' glycaemic control and mental health symptoms have important and independent associations with diabetes-related symptom burden. Findings

Table 1. Baseline patient sociodemographic and health status characteristics [percent or count/mean (SD), *N*=710[a]]

Patient characteristics[b,c]	Low depressive symptoms (*n* = 325)[d]	High depressive symptoms (*n* = 385)	*P* value
Age, years	58.0 (11.2)	57.7(11.2)	0.69
Race, % Non-Hispanic white	17.5	16.3	0.67
% Hispanic	64.3	59.7	0.21
% Vietnamese	18.1	23.9	0.06
Gender, % male	42.7	37.7	0.16
Education, % more than high school	26.1	22.9	0.33
Burden from comorbid illness, mean	3.0 (2.2)	5.6 (3.3)	<.001
HbA1C, %	8.0 (1.7)	8.3 (1.6)	0.19
Hypoglycaemic symptoms	1.9 (1.2)	2.8 (1.4)	<.001
Hyperglycaemic symptoms	2.7 (1.6)	3.4 (1.4)	<.001

[a]Of the 773 eligible patients who completed the year 1 follow-up, 63 patients were missing data on HbA1C. Thus, the sample size used for all analyses noted in the manuscript is 710.

[b]Values presented as means with standard deviations in parenthesis for continuous variables and as percentages for categorical variables. *P* values for group comparisons were computed using independent samples *t*-tests for continuous variables and χ^2 tests for categorical variables.

[c]Age, race/ethnicity, gender, education, burden from comorbid illness and hypoglycaemic and hyperglycaemic symptoms were derived from the patient questionnaire. HbA1c was derived from the baseline medical record abstraction.

[d]Depressive symptomatology was derived from the patient questionnaire. A cut-off score of ≥22 was used to indicate high depressive symptoms, which has been used among chronically ill patients (14) to indicate clinically relevant levels of depressive symptoms.

Table 2. Relative contribution of mental health symptoms to diabetes-related symptom burden: findings from two hierarchical linear regressions predicting patient-reported hypoglycaemia (Model 1) and hyperglycaemia (Model 2)

	Diabetes-related symptom burden[a,b]							
	Model 1 (N = 625): hypoglycaemic symptoms				Model 2 (N = 643):hyperglycaemic symptoms			
	Step 1:		Step 2:		Step 1:		Step 2:	
	β (t)	P value	β (t)	P value	β (t)	P value	β (t)	P value
Insulin use by patient[c]	0.15 (3.78)	<0.001	0.14 (3.56)	<0.001	0.10 (2.68)	0.008	0.10 (2.54)	0.01
Haemoglobin A1C	−0.10 (−2.33)	0.02	−0.11 (−2.46)	0.01	0.11 (2.70)	0.007	0.11 (2.66)	0.008
Burden from co-morbid illness	0.31 (8.39)	<0.001	0.23 (5.50)	<0.001	0.34 (9.54)	<0.001	0.29 (7.27)	<0.001
Depressive symptoms			0.17 (3.94)	<0.001			0.09 (2.22)	0.02
Model fit, adjusted R^2(P value)	0.15, P < 0.001		0.18, P < 0.001		0.21, P < 0.001		0.22, P < 0.001	

[a]Two separate hierarchical linear regressions were conducted to examine diabetes-related symptom burden as assessed by patient reports of hypoglycaemia and hyperglycaemia. Standarized β's reported.

[b]Analyses also included the following variables as covariates: race/ethnicity, gender, age and education level.

[c]Insulin use was assessed from review of medical records from the baseline year.

Table 3. Predicting physician medication prescribing behaviours from diabetes-related symptom burden for patients with high versus low depressive symptoms

	Any intensification of a diabetes-related medication in year 1	
	Adjusted odds ratio (95% CI)	P value
Model 1		
Haemoglobin A1C	1.24 (1.10, 1.39)	<0.001
Patient-reported hypoglycaemia	1.24 (0.98, 1.58)	0.08
Depressive symptoms	1.03 (1.00, 1.05)	0.01
Hypoglycaemia × depressive symptoms	0.98 (0.97, 0.99)	0.03
Model 2		
Haemoglobin A1C	1.23 (1.09, 1.39)	<0.001
Patient-reported hyperglycaemia	1.21 (1.00, 1.46)	0.05
Depressive symptoms	1.03 (1.01, 1.05)	0.04
Hyperglycaemia × depressive symptoms	0.99 (0.98, 1.00)	0.09

[a]Two separate logistic regressions were conducted to examine any intensification of a diabetes-related medication in the year following the baseline assessment.

[b]Analyses included adjustment for standard demographic characteristics (including race/ethnicity, gender, age and education), insulin use by patient and burden from comorbid illness.

from this study also suggest that physicians' decisions to adjust patients' medications may differentially be associated with patient-reported diabetes-related symptom burden for patients with lower versus higher levels of depressive symptoms. Specifically, the findings suggested that the likelihood of having a physician intensify the diabetes treatment was lowest for patients who experienced both a high frequency of hypoglycaemic symptoms and high depressive symptoms. What remains unanswered is the extent to which physicians were aware of patients' mental health status, and thus whether this difference reflected a conscious choice, or whether physicians were acting cautiously for another reason. In contrast, patients who experienced a high frequency of hyperglycaemic symptoms were more likely to have their medication intensified, independently of actual level of glycaemic control and their level of depressive symptoms.

Taken together, these findings highlight the importance of physicians addressing the connection between diabetes and comorbid mental health to ensure that patients' reports of diabetes-related symptoms are interpreted appropriately.

Previous studies have shown that, among patients with diabetes, comorbid depression contributes to poor metabolic control, decreased quality of life and increased morbidity and mortality (7,17–19). Evidence from prospective and cross-sectional studies indicates that depressive symptoms have been associated with factors related to glucose dysregulation (20,21), including obesity and non-adherence to dietary and medication treatment recommendations, which, in turn, increase patients' risk of diabetic complications (22). This study suggests that increased diabetes-related symptom burden may also play an important role in this link between depressive symptomotology and suboptimal diabetes outcomes. For example, providers appear to make different choices about intensifying a patient's medications as a function of both patients' symptom burden, particularly patient reports of hypoglycaemia, as well as patients' mental health status, at a similar HbA1c level.

Over time, most people will require progressively intensified pharmacologic therapy to achieve recommended glycaemic targets (23). In the present study, physicians' decisions to modify therapy were found to be driven, in part, by patients' reports of their diabetes-related symptoms, independent of the level of glycaemic control. Addressing depressive symptoms may help physicians better gauge the appropriate response to elevated diabetes-related symptoms with respect to the diabetes medication regimen. This is of particular importance among racial/ethnic minorities, given that primary care physicians often are the first point of professional contact with whom patients discuss mental health concerns (24,25) and that somatizing mental health symptoms is common (5,6).

Limitations

Limitations of this study should be noted. First, depressive symptoms were assessed using the CES-D, which may reflect general psychological distress, rather than a clinical diagnosis of major depressive disorder. Given that patients who exhibit high levels of depressive symptoms experienced worse diabetes-related symptoms, efforts to treat these symptoms are important nonetheless in order to alleviate the adverse effects on diabetes outcomes. Furthermore, it is difficult to determine whether the causes of somatic symptoms are psychological or organic. Despite the underlying cause of these symptoms,

they contribute significantly to diabetes-related complications and thus require attention. Second, both hypoglycaemia and hyperglycaemia were not objectively verified, and the self-report was elicited on a single occasion, asking respondents to reflect back over a 6-month time period. Nonetheless, work by McCoy and colleagues has shown that self-reported severe hypoglycaemia has been associated with a 3.4-fold greater risk of 5-year mortality compared with mild or no hypoglycaemia, highlighting the importance of considering patient-reported symptom burden as an unique and important part of patients' health information (12). Third, specific reasons why patients' medications were changed are not known. In addition to responding to changes in patients' glycaemic control, other factors, such as reported side effects and cost, influence a providers' decision to change patients' medications (26). Finally, findings from this study examining the associations between depressive symptoms and patient-reported symptom burden are cross-sectional, and thus preclude our ability to determine the causal order of these two relationships under investigation. For example, the cause-and-effect relationship between antidepressants and glucose metabolism is still unclear, with there being some evidence of the hyperglycaemic effects of some antidepressants (27). Most antidepressant medications, including tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and mirtazapine, increase levels of monoaminergic serotonin and norepinephrine, and modify the balance of the hypothalamus-pituitary-adrenal (HPA) axis known to be associated with depression as well as insulin resistance (28). Further efforts are needed to disentangle the temporal order of effects of medication, HbA1C, and mental health symptoms on diabetes-related symptom burden. Poor glycaemic control may adversely affect mood and thereby reinforce the relationship between diabetes and depression (20,29).

Implications/relevance for diabetes educators

In summary, the findings from this study suggest that among patients with type 2 diabetes, physicians need to focus on identifying and treating mental health symptoms. Given the interconnection of depression and diabetes-related symptoms (3,7), treating patients' depressive symptoms may lead to a more accurate assessment of symptom burden, and therefore, better guidance for treatment. Evidence suggests, however, that the rates of diagnosis and treatment of depression in primary care is low, particularly among racial/ethnic minorities (5). These low rates may be further compounded by language barriers to effective patient–provider communication of mental health concerns (30). Thus, interventions should be both culturally and linguistically tailored to improve the discussion of mental health issues of all patients with diabetes. Addressing these mental health concerns can help guide treatment to maximize patient outcomes.

Declaration

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