Longitudinal effect of depression on glycemic control in patients with type 2 diabetes: a 3-year prospective study

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Objectives
The aim of this study was to examine the longitudinal effect of depression on glycemic control in a sample of patients with type 2 diabetes.
Patients and methods
Patients were recruited from the diabetes clinic in Saudi Airlines Medical Centre, Jeddah; the baseline study community consisted from 172 patients with type 2 diabetes. They were assessed for depression using Beck Depression Inventory-II and a diagnostic interview and for diabetic control using HbA1c. We created a person–period dataset for each patient to cover 6-month intervals up to 3 years. We used the generalized estimation equation (GEE) for the analysis of longitudinal data. HbA1c was the response variable, whereas depression and time were the main covariates. Variables were included in GEE models based on clinical importance and preliminary analysis. Other variables included as covariates were sex, education, duration of diabetes, comorbidity, and Low-density Lipoprotein (LDL). All statistical analyses used an α-value of 0.05 as the level of significance and were performed using SPSS software version 21.
Results
Unadjusted HbA1c means were significantly higher in depressed as against nondepressed individuals at all time points. Adjusted HbA1c means in the final GEE model were significantly higher in depressed as against nondepressed individuals. In all adjusted models, depression was a significant predictor of glycemic control, whether it was measured as the Beck Depression Inventory score (estimate=0.049, P=0.002) or diagnoses of major depressive disorder (estimate=2.038, P=0.000) or other depressive disorders (estimate=1.245, P=0.000).
Conclusion
This study on a clinical sample of type 2 diabetic patients demonstrates that there is a significant longitudinal relationship between depression and glycemic control and that depression is associated with a persistently higher HbA1c over time.

Keywords:
depression, depressive disorders, diabetes, diabetic control, hba1c, major depressive disorder, type 2 diabetes

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to insulin deficiency. The diagnosis of diabetes is a life-threatening stressor that demands high mental and physical accommodations (Ganasegeran et al., 2014).

The International Diabetes Federation estimated that more than 371 million people (8.3% of the adult population worldwide) had diabetes in 2012 (International Diabetes Federation, 2013). Projection rates of diabetes are expected to increase to over 438 million by the year 2030 (Khuwaja et al., 2010). Diabetes is currently ranked as the 14th leading cause of global disease burden, and has moved up several places in the rankings for leading causes since 1990; however, major depression is currently ranked the 11th leading cause of global disease burden, and it has also moved up several places in the rankings for leading causes since 1990 (Murray et al., 2012).

Diabetes is often comorbid, with clinically relevant symptoms of depression (Katon et al., 2004; Atlantis et al., 2014). People with diabetes are twice as likely to be depressed as people without chronic disease (Anderson et al., 2001; Trief et al., 2006). Clinical and subclinical expressions of depression range between 11% (Anderson et al., 2001) and 40% (Ganasegeran et al., 2014) in patients with diabetes.

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Depression is a risk factor for the onset of type 2 diabetes (Knol et al., 2006; Llyod et al., 2010) and is associated with hyperglycemia, poor metabolic control, higher complication rates, smoking, and increased all-cause mortality (Ciechanowski et al., 2000; Clouse et al., 2003; Egede, 2004; McKellar et al., 2004; Egede et al., 2005; Zhang et al., 2005; Richardson et al., 2008).

Depression among people with diabetes adds an increased burden to patient adherence, compliance, and poor prognosis for quality health outcomes (Ciechanowski et al., 2000; Ganasegeran et al., 2014). It has adverse effects on functioning and quality of life, increases hospital days, and days off work (Lustman et al., 2000; Egede and Zheng, 2003; Fisher et al., 2007a, 2007b), and gives rise to challenges in patient care and medical costs (Egede et al., 2002; Lin et al., 2012; Atlantis et al., 2014).

Clearly, the co-occurrence of diabetes and depression has significant implications for clinical outcomes, disease management, healthcare costs, and patient health and well-being (Fisher et al., 2007a, 2007b); there is some evidence that depression worsens glycemic control because it worsens self-care (Hampson et al., 2000; Katon et al., 2009).

Numerous cross-sectional studies have found depression to be associated with poor glycemic control (Karlsson et al., 1988; Niemcryk et al., 1990; Von Dras and Lichty, 1990; Lee et al., 1996; Trief et al., 2006), and some found a stronger significant correlation between major depression (not minor depression or dysthymia) and higher A1c (Katon et al., 2004; Abuhegazy et al., 2014), although a systematic review of cross-sectional studies had demonstrated a significant small-sized to medium-sized correlation between depression and A1c and a trend for depression to predict A1c (Lustman et al., 2000).

Of the few prospective studies (Mazze et al., 1984; Katon et al., 2005; Nakahara et al., 2006; Trief et al., 2006; Ismail et al., 2007; Richardson et al., 2008), only one (Richardson et al., 2008) demonstrated a clear association between depression and persistently high HbA1c levels over a 4-year period in patients with type 2 diabetes, whereas another study (Mazze et al., 1984) found such a correlation in patients with type 1 diabetes.

The aim of this study was to investigate the longitudinal effect of depression on glycemic control over a 3-year period. According to current evidence, we hypothesized that (a) depression would be associated with higher HbA1c in adults with type 2 diabetes over time and (b) the effect of depression on glycemic control would persist over time.

Patients and methods

Patients

Participants were recruited from adult patients (18–65 years old) diagnosed with type 2 diabetes and regularly followed through the outpatient diabetes clinic in the Saudi Arabian Airline Medical Center in Jeddah, Saudi Arabia. We approached 224 patients: 21 of them refused participation, and 23 were excluded because they fulfilled one or more of the following exclusion criteria:

(1) The type of diabetes is indeterminate from the medical records and/or consultation with the physician.
(2) Patients with a history of stroke, brain surgery, closed head injury, dementia, pregnancy, or illness that could affect glucose control.
(3) Patients who are unable to complete the Beck Depression Inventory (BDI) questionnaire (Arabic version) independently because of visual disability or a primary language other than Arabic.

The baseline community consisted of 172 adult patients with type 2 diabetes; they were followed up for 36 months. A total of 21 participants were lost to be contacted through the follow-up period, leaving an endpoint community of 151 participants. There were no significant differences between patients who declined participation, those lost to follow-up, and patients who completed the study with regard to their age, sex, or clinical characteristics.

Procedures

After informed consent, all baseline patients were interviewed to collect their personal and demographic data; patients were asked to complete the BDI-II during the interview.

All data about their illness, which were obtained from medical records, were reviewed and completed by a diabetic physician, including the duration of diabetes, types of medications, diabetic complications, medical comorbidities, recent infections, other medical conditions, and medications that may affect glucose control. A full laboratory make up including fasting blood glucose, HbA1c, and full lipid profile was performed (either obtained from medical records if it was performed within 3 months or newly

requested). All patients were interviewed by a consultant psychiatrist for a mental state examination and diagnosis according to DSM-IV-TR (the psychiatrist was unaware about the BDI scores). Proper action was carried out for all patients found to have clinical depression or other psychiatric morbidities.

For the purpose of follow-up analyses, we created a person–period data set for each patient to cover 6-month intervals; we chose 6-month intervals because HbA1c is generally measured every 3–6 months; six time intervals were created to cover a total period of 3 years. The study was carried out between March 2009 and September 2012.

One HbA1c value for each patient in the 6-month time interval was used for analyses; for patients with two or more HbA1c values in a given 6-month interval, the most recent was used for analyses.

All procedures were approved by the research and ethics committee of the Saudi Airlines Medical Center.

Outcome measures

Depressive symptoms were assessed by the Arabic version of the BDI-II (The Psychological Corporation, Orlando, Florida, USA). BDI-II has been shown to have high reliability and validity (Beck et al., 1961); it is widely used to assess depression in both community and clinical samples; furthermore, BDI has been validated as a tool for measuring depression in diabetic patients (Wing et al., 1990; Leedom et al., 1991; Lustman et al., 1997). BDI has been translated into Arabic by Abdel-khalek and has shown high reliability and validity also. Scores of 16 and above were used as a cutoff point for probable depression and 25 and above for confirmed depression (Abdel-khalek, 1998).

Clinical depression was assessed by a direct interview performed by a consultant psychiatrist with sufficient experience, and patients were diagnosed according to the DSM-IV-TR classification.

Glycemic control was assessed by both fasting blood glucose and HbA1c.

Statistical analysis

We performed three sets of analyses. First, we used the two-tailed *t*-test for continuous variables and the χ^2-test for categorical variables to examine differences between depressed and nondepressed individuals with type 2 diabetes regarding sociodemographic and clinical variables.

Second, we used a pooled *t*-test to compare unadjusted mean HbA1c across at all time points for depressed against nondepressed individuals with type 2 diabetes.

Third, we used the generalized estimation equation (GEE) for analysis to account for within-subject correlations that present in longitudinal data (follow-up of HbA1c over 36 months). GEE takes into account the dependence of observations by specifying a 'working correlation structure'. We explored the missing data pattern and mechanism by little's methods, which revealed that the missing data are completely at random. Hence, using GEE, there was no need for impu tation of missing data. Variables were included in GEE models on the basis of clinical importance and preliminary analysis. In GEE, HbA1c was the response variable, whereas depression and time were the main covariates. We performed two models where depression was examined using two different measurement approaches (BDI score and clinical diagnosis). Other variables included as covariates were sex, education, duration of diabetes, comorbidity, and LDL. All statistical analyses used an α-value of 0.05 as the level of significance and were performed using SPSS software version 21 (Armonk, NY: IBM Corp.).

Results

Out of the 224 eligible patients approached, 21 declined to participate, 23 were excluded because they fulfilled one or more of the exclusion criteria (being illiterate, primary language not Arabic, have serious comorbid conditions), and eight patients were excluded because their diabetes type was indefinite. Out of the potential participants, only 172 patients were enrolled in the baseline analyses.

For the prospective analyses, 21 participants were lost to be contacted; only 151 participants completed the 36-months follow-up assessments. There were no significant differences between patients who completed the 3-year assessment and those who did not with regard to their age, sex, or baseline medical data.

Detailed analyses of the baseline results have been shown in earlier reports. Limited data are provided here to provide a context for this study.

Baseline correlates of depression

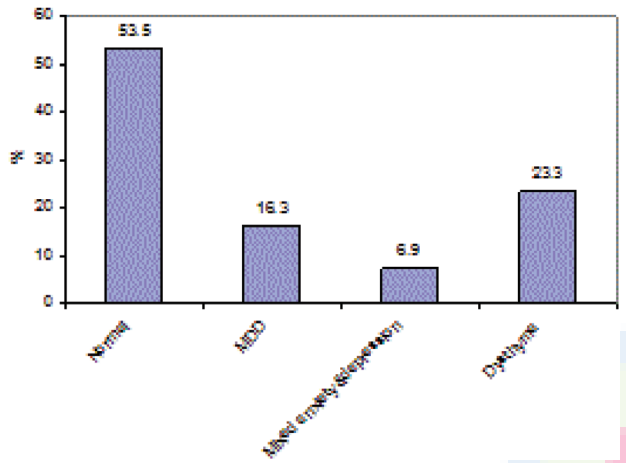
The baseline mean BDI score was 14.8 (SD=8.9): 16.3% of the patients were diagnosed with major depressive disorder (MDD), whereas 30.3% were diagnosed with other depressive disorders (Fig. 1). Baseline analyses showed a significant correlation between depression and HbA1c. Patients with comorbid depression and type 2 diabetes were mostly female (P=0.009), less educated

(*P*=0.000), with higher fasting blood glucose (*P*=0.000), HbA1c (*P*=0.010), and triglycerides (*P*=0.006).

Baseline predictors of glycemic control

Unadjusted correlation between depression and glycemic control showed that there was a significant linear correlation between BDI scores and HbA1c (*r*=0.17, *P*=0.02). After adjustment for all other covariates in the regression models, MDD and probable severe depression (BDI score>25), but not the entire range of BDI scores, were significant predictors of higher HbA1c (estimate=0.15, *P*=0.03; and estimate=0.12, *P*=0.04, respectively). Also, the duration of diabetes was the most important predictor of HbA1c (estimate=0.52, *P*=0.000).

Figure 1



Clinical diagnosis of the baseline sample.

Prospective study patients' characteristics

Table 1 shows the demographic and clinical charact eristics of the endpoint study participants. About 70.9% of them were male; their mean age was 51.9 (SD=6.4) years, the majority had intermediate education (60.9%), more than half were employed (55%), and 42.4% of them were smokers. Regarding their clinical assessment data, the mean BMI was 32.2 (SD=5.8), the mean duration of diabetes was 10.3 (SD=3.5) years, 94.7% were receiving oral diabetic medications, the mean Fasting Blood Sugar (FBS) was 179.9 (SD=7.4), and the mean HbA1c was 8.7 (SD=2.1).

Prospective analyses of depression as a predictor of glycemic control

Figure 2 shows unadjusted mean HbA1c values for depressed and nondepressed patients at each of the six follow-up time points, respectively. Unadjusted mean HbA1c values for depressed patients were consistently and significantly higher than those of nondepressed patients with type 2 diabetes at all follow-up time points (36 months) [mean HbA1c=9.1 {95% confidence interval (CI) 8.8–9.7} vs. 8.2 (95% CI 7.9–8.8), respectively; mean difference=0.9, *P*=0.000].

Table 1 Descriptive statistics of the prospective study sample according to DSM-IV diagnosis

Characteristics	All sample (*n*=151)	Nondepressed (*n*=82)	Depressed (*n*=69)	*P* value
Sex [*n* (%)]				
Male	107 (70.9)	66 (80.5)	41 (59.4)	0.005*
Female	44 (29.1)	16 (19.5)	28 (40.6)	
Level of education [*n* (%)]				
Illiterate	4 (2.6)	4 (4.9)	0 (0)	0.000*
Read and write	12 (7.9)	0 (0)	12 (17.4)	
Intermediate	92 (60.9)	48 (58.5)	44 (63.8)	
High	43 (28.5)	30 (36.6)	13 (18.8)	
Employment [*n* (%)]				
None	68 (45)	40 (48.8)	28 (40.6)	0.313
Employed	83 (55)	42 (51.2)	41 (59.4)	
Smoking [*n* (%)]				
No	87 (57.6)	48 (58.5)	39 (56.5)	0.803
Yes	64 (42.4)	34 (41.5)	30 (43.5)	
Medication for diabetes [*n* (%)]				
Insulin	8 (5.3)	4 (4.9)	4 (5.8)	0.802
Oral	143 (94.7)	78 (95.1)	65 (94.2)	
Age (years) (M±SD)	51.9±6.4	51.9±6.4	50.2±4.8	0.081
BMI (M±SD)	32.2±5.8	31.3±5.3	33.2±6.2	0.053
Duration of diabetes (M±SD)	10.3±3.5	10.5±3.8	9.9±6.6	0.596
FBS (M±SD)	176.9±7.4	163.1±5.4	193.3±6.8	0.007*
HbA1c (M±SD)	8.7±2.1	8.2±2.2	9.1±2.1	0.034*
LDL (M±SD)	99.6±38.4	91.5±35.5	102.6±39.8	0.105

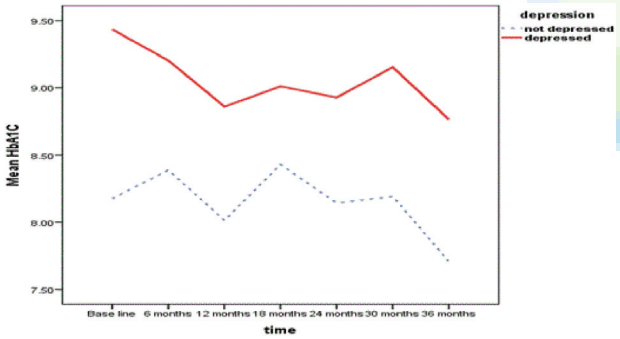
*Significant *P* value of χ^2-test or *t*-test≤0.05.

Table 2 shows the results of GEEs for HbA1c as the dependent variable and depression (measured as BDI score or DSM-IV diagnoses) as the main covariate adjusted for time, sex, education, comorbidity, duration of diabetes, and LDL-cholesterol.

Results revealed that the BDI score was a significant predictor of HbA1c follow-up (estimate=0.049, *P*=0.002). A 1 U increase in the BDI score leads to 0.07 increase in HbA1c level. There was no significant change in HbA1c over time (*P*=0.103). The interaction between time and depression was not significant (*P*=0.602), which means that there was no significant difference in the change in HbA1c values over time corresponding to the values of BDI score in type 2 diabetics. Results also revealed that both MDD and other depressive disorders were significant predictors for HbA1c follow-up (estimate=2.038, *P*=0.000 and estimate=1.245, *P*=0.000, respectively). This indicates that values of HbA1c in depressed patients were significantly and consistently higher than those in nondepressed individuals. The adjusted mean of HbA1c for depressed individuals is 8.8 (95% CI 8.2–9.1) against 7.7 (95% CI 7.5–8.3) for nondepressed individuals, with mean difference of 1.1 and *P* value of 0.000. Time was not a significant predictor of change in HbA1c (estimate=–0.004, *P*=0.713). The interaction between time and depression was not significant (*P*=0.248), which means that there was no significant difference in the change in HbA1c values over time for depressed against nondepressed type 2 diabetes patients.

Other significant longitudinal predictors for higher follow-up HbA1c values were comorbidities (ES=0.607, *P*=0.01; and ES=0.484, *P*=0.044) (which means that patients with DM and comorbid disorders had a higher HbA1c at follow-up), DM duration (ES=0.064, *P*=0.000; and ES=0.066, *P*=000) (which means that patients with a longer duration of DM had a higher HbA1c), and LDL (i.e. patients who had higher levels of LDL had a higher HbA1c at follow-up) (ES=0.008, *P*=0.006; and ES=0.012, *P*=0.000).

Figure 2



Unadjusted mean HbA1c over time in depressed and nondepressed type 2 diabetic patients.

Discussion

This study of patients with type 2 diabetes demonstrates that there is a significant longitudinal relationship between depression and glycemic control as measured by HbA1c, and that depression is associated with persistently higher HbA1c levels over a 3-year follow-up. This is the second study to our knowledge to show this longitudinal association between depression and glycemic control. The first was a large-scale population-based cohort study on patients with type 2 diabetes, which found a significant association between depression and glycemic control, and that depression was associated with persistently higher A1c levels over a mean time of 4 years (Richardson et al., 2008); however, other longitudinal studies did not demonstrate a similar relation (Katon et al., 2005; Nakahara et al., 2006; Trief et al., 2006; Ismail et al., 2007).

Table 2 Generalized estimating equations for HbA1c as the response variable and depression as the main covariate

	BDI (*n*=151)			DSM-IV diagnoses (*n*=151)		
	β-Coefficient estimate	SE	*P* value	*β*-Coefficient estimate	SE	*P* value
Intercept	5.880	0.4637	0.000*	5.003	0.5012	0.000*
Depression (reference category none)	0.049	0.0160	0.002*	2.038[a]	0.4070	0.000*
				1.245[b]	0.3561	0.000*
Time	–0.070	0.0426	0.103	–0.004	0.0113	0.713
Sex (reference category female)	–0.150	0.3392	0.658	–0.238	0.3428	0.488
Education (reference category not educated)	0.361	0.4696	0.441	0.634	0.4752	0.182
Comorbidity (reference category no)	0.607	0.2351	0.010*	0.484	0.2402	0.044*
DM duration	0.064	0.0171	0.000*	0.066	0.0179	0.000*
LDL	0.008	0.0029	0.006*	0.012	0.0026	0.000*
Depression×time (interaction)	0.001	0.0018	0.602	–0.145	0.0565	0.010*

BDI, Beck Depression Inventory; DM, diabetes mellitus. [a]Major depressive disorder (MDD). [b]Other depressive disorders. *$P<0.05$, statistically significant.

The study shows that depressive symptoms as measured by BDI are a significant predictor for HbA1c at follow-up, and shows that a 1-U increase in the BDI score leads to a 0.07 increase in the HbA1c level; this is the first study to our knowledge to show this longitudinal association between depressive symptoms and diabetic control in type 2 diabetes patients. Prior studies that found a similar relation were cross-sectional in nature (Karlsson et al., 1988; Niemcryk et al., 1990; Von Dras and Lichty, 1990; Lee et al., 1996; Trief et al., 2006; Abuhegazy et al., 2014). The absolute increment in HbA1c values in response to the increase in BDI scores appears to be small to medium; this is consistent with the results of large meta-analyses of cross-sectional studies (Lustman et al., 2000), which found that the association between depression and glycemic control was larger when standardized interviews and diagnostic criteria rather than self-report questionnaires were used to assess depression (ES=0.28 vs. 0.15), perhaps because the relationship may be stronger in patients with clinical depression than in those with subclinical depression. Self-report inventories are also less specific measures of depression, as elevated scores may be produced not only by depression but also by anxiety, general emotional distress, or medical illness.

The study shows that depressive disorders are associated with persistently higher HbA1c levels over time, with the mean difference between depressed and nondepressed patients being 0.9% in unadjusted and 1.1% in adjusted models, which seems to be a relatively large difference and is likely to have clinically relevant effects. A previous study (Richardson et al., 2008) had found a mean difference of 0.13%, which seems to be a small difference. This discrepancy may be explained by the differences in glycemic control as well as differences in variability of HbA1c values between the samples of the two studies; baseline HbA1c in our study sample was 8.7% against 7.3% in the Richardson study.

A cross-sectional analyses of the same patients' data had revealed that after full adjustment, only patients with diabetes and comorbid severe depressive symptoms (BDI score>25), but not the entire range of BDI scores, and MDD were significant predictors of higher HbA1c (P=0.046 and 0.034, respectively) (Abuhegazy et al., 2014). This is in contrast to the IDEATel study on elderly patients, which found significant correlation between depression and HbA1c at baseline and a trend for depression to predict A1c when other factors were controlled; however, in prospective analyses, depression did not predict changes in HbA1c over a 1-year follow-up (Trief et al., 2006). The difference in the trend of the effect of depression on diabetic control over time may be accounted for by the age group differences, which may be an important reason for such discrepancies. Numerous studies have found that the prevalence of depression is higher among younger patients with type 2 diabetes (Anderson et al., 2001); others have found that higher HbA1c levels are associated with major depression in younger but not older patients (Lustman et al., 2000). There may be a survivorship effect such that younger patients who do not follow self-care regimens or who have a more severe disease do not live to be older, and the endocrine physiology of developing diabetes in later life may also differ from younger onset patients (Katon et al., 2004). the duration of disease itself may offer another explanation for this discrepancy, although it has been demonstrated that a longer duration of diabetes is associated with higher odds of depression (Lustman et al., 2000), the duration of diabetes was the most significant independent predictor of poor glycemic control in both cross-sectional (ES=0.52, P=0.000) and longitudinal analyses (ES=0.066, P=0.000) of this patients population. This finding indicates that the effect of depression in our sample tends to be sustained over time, and moreover, it tends to be deeper and wider.

This large difference of HbA1c between depressed and nondepressed individuals (1.1%) and its sustainability over a relatively long duration (3 years follow-up) is likely to have clinically relevant effects. Findings from UKPDS trials have demonstrated that lower HbA1c is associated with greater odds of slowing or preventing the development of serious eye, kidney, or nerve diseases, and that any improvement in HbA1c levels can reduce complications (UK Prospective Diabetes Study (UKPDS) Group 1998a, 1998b). Moreover, the EPIC-NORFOLK study found that HbA1c was continuously related to subsequent all-cause mortality, and there was a significant linear relationship between HbA1c levels and the risk of death across varying levels of HbA1c (Khaw et al., 2001).

These findings might explain the clinical importance of depression in the outcome of diabetes, as it persistently increases HbA1c, leads to numerous poor outcome consequences such as increased complication rates, high healthcare utilization and costs, adverse effects on functioning and quality of life, increased hospital days and days off of work, and has a higher risk of morbidity and mortality (Ciechanowski et al., 2000; Lustman et al., 2000; Clouse et al., 2003; Egede, 2004; McKellar et al., 2004; Fisher et al., 2007a, 2007b).

It is worth mentioning that the prevalence of depressive disorders in this study reaches 16.3% for MDD and 30% for other depressive diagnoses (dysthymia, and mixed depression and anxiety disorder); this finding is in concordance with a large meta-analyses of prevalence of depression in adults with diabetes by Anderson et al., 2001, which included 42 studies and found the prevalence of depression in clinical samples to be 32.7%, which decreases by using structured interviews to 14.2% and increases by using self-report instruments up to 34.9%; also, an earlier study by Gavard et al., 1993 found major depression in 14.7% and elevated depression symptoms in 26% of diabetic patients. The prevalence of depression varied systematically as a function of the method used to identify depression cases and the study design. It is likely that the two approaches identify somewhat different but overlapping samples of depressed individuals. Diagnostic interviews identify MDDs, but exclude other clinically relevant presentations, whereas self-report measures may identify a broader spectrum of depression disorders (e.g. dysthymic disorder or minor or subsyndromal depression) or symptoms that reflect comorbid psychiatric illness (e.g. anxiety or substance-abuse disorders) or general distress (Anderson et al., 2001). A semistructured interview may be able to capture both.

Strengths of this study include the prospective design, the longitudinal data, and the availability of data on HbA1c, comorbidity, and other clinical and confounding factors. Another strength of this study is that the diagnosis of diabetes was confirmed by direct clinical diagnoses and follow-up data, and depression has been identified by a self-report questionnaire and clinical diagnoses according to DSM-IV-TR. However, the study has some limitations: first, the clinical sample of depressed patients may not represent the general population because they are mostly men (70.9%) and also due to changes in help-seeking behavior; the other limitation is the influence of confounding factors that cannot be fully accounted for. This study confirms the association of depression with hyperglycemia, but reveals neither the mechanism nor the direction of the association. Depression may be a cause or a consequence of hyperglycemia; the causal mechanisms underlying these pathways may or may not be the same, and both the direction and the mechanism may vary over time, between episodes, and both between and within individuals (Chen et al., 2013). This issues as well the issue of the effect of management of depression on the diabetic outcome should be addressed further, especially through designed case–control longitudinal studies.

Conclusion

This prospective study on a clinical sample of type 2 diabetic patients demonstrates that there is a significant relationship between depression and glycemic control, and that depression is associated with persistently higher HbA1c over time.

Recommendations

It is recommended to add psychological assessment for diabetic patients in the diabetic clinic by a psychologist to identify any depressive symptoms among them by validated depressive scales and refer them to a psychiatrist if needed to mitigate such comorbidities and lessen the patient's burden.

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Conflicts of interest

There are no conflicts of interest.

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