Diabetes and Depression: Global Perspectives

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Abstract

Background: Diabetes and depression are highly prevalent chronic conditions that have significant impact on health outcomes. The objective of this study was to review the literature on the prevalence, burden of illness, morbidity, mortality and cost of co-morbid depression in people with diabetes as well as the evidence on effective treatments.

Methods: Systematic review of the literature on the relationship between diabetes and depression was performed. A comprehensive search of the literature was performed on Medline from 1966 to 2009. Studies that examined the association between diabetes and depression were reviewed. A formal meta-analysis was not performed because of the broad area covered and the heterogeneity of the studies. Instead, a qualitative aggregation of studies was performed.

Results: Diabetes and depression are chronic debilitating conditions that are associated with significant morbidity, mortality, and healthcare costs. Coexisting depression in people with diabetes is associated with decreased adherence to treatment recommendations, poor metabolic control, higher complication rates, decreased quality of life, increased healthcare use and cost, increased disability and lost productivity, and increased risk of death.

Conclusion: The coexistence of diabetes and depression is associated with significant morbidity, mortality and increased healthcare cost. Coordinated strategies for clinical care are necessary to improve clinical outcomes and reduce the burden of illness.

Global burden of diabetes

Reports from the International Diabetes Federation (IDF) indicate that the prevalence of diabetes mellitus has reached epidemic levels globally. Estimates for 2010 indicate that 285 million adults have diabetes in the seven regions of the IDF [1]. These numbers represent an increase of 39 million from 2007 and an expected continued increase to 439 million in 2030 [1]. Given prevalence figures approaching 290 million, the worldwide human, economic, and social costs of diabetes are staggering. For example the IDF estimates that 3.9 million deaths will be caused by diabetes in 2010 which represents 6.8% of the total global mortality [1]. It is also believed that by 2025, more than 75% of the world population with diabetes will reside in developing countries and the countries with the largest populations of adults with diabetes will include: India, China and the United States [2]. In developing countries, the majority of adults with diabetes are between 45 and 64 years old, whereas in developed countries the majority of adults with diabetes are 65 years and older [2]. The IDF estimates that 23 million years of life are lost to disability and reduced quality of life as a result of complications associated with diabetes [3]. The costs associated with diabetes are difficult to accurately capture but some estimates suggest that USD232 billion were spent worldwide in 2007 to treat and prevent diabetes and this number is expected to climb to a minimum of over USD300 billion in 2025 [3]. In the United States alone, the total cost of diabetes was reportedly USD132 billion in 2002 [4] while estimates from smaller and more economically disadvantaged countries such as Tanzania are USD2.5 billion [3].

Global burden of depression

Depression is another condition with high prevalence worldwide. Approximately 340 people worldwide suffer from depression at any given time including 18 million in the United States [5]. According to the World Health Organization (WHO), depression is responsible for the greatest proportion of burden associated with non-fatal health outcomes and account for approximately 12% of total years lived with disability [6]. In 2000, it was estimated that depressive disorders were higher in women (4930 per 100,000) than men (3199 per 100,000) and that, globally, depressive disorders were the fourth leading cause of disease burden in women and seventh leading cause in men [7]. The World Mental Health Survey was conducted to estimate the 12-month prevalence rate of mood, anxiety and alcohol-use disorder among community samples of adults across 17 countries including: Europe, the Americas, the Middle East, Africa, Asia and the South Pacific [8]. Among more than 85,000 adults surveyed, 42,697 self-reported the presence of diabetes. The risk of mood and anxiety disorders was higher among individuals with diabetes relative to those without. The odds ratio for depression was 1.38 (95% CI 1.14-1.66) after adjusting for age and gender.

Recent studies have reported that the lifetime prevalence of a major depressive disorder in the United States was 16.2% [9] whereas the lifetime prevalence in Europe was 14% [10]. A third study designed to examine the prevalence of mood disorders in 14 countries in the Americas, Europe, Middle East, Africa and Asia found that the 12-month prevalence of mood disorders was 0.8% in Nigeria, 3.15% in Japan, 6.6% in Lebanon, 6.8% in Columbia, 6.9% in the Netherlands, 8.5% in France, 9.1% in the Ukraine and 9.6% in the United States [11]. Studies show that depression is a major cause of morbidity, mortality and disability [12] and is associated with workplace absenteeism, diminished or lost work productivity and increased use of healthcare resources [13]. Finally, major depression is the second leading cause of disability-adjusted life years (DALYs) lost in women and the tenth leading cause of DALYs in men [12].

Depressive disorders include major depression, minor depression and dysthymia. The clinical diagnosis of major depression is based on the presence of depressed mood and anhedonia during the same two-week period and the presence of any five of the following symptoms [14]: i) depressed mood; ii) markedly diminished interest or pleasure in activities; iii) significant weight loss when not dieting or weight gain; iv) insomnia or

hypersomnia; v) psychomotor agitation or retardation; vi) fatigue or loss of energy; vii) feelings of worthlessness or excessive or inappropriate guilt; viii) diminished ability to think or concentrate; and ix) recurrent thoughts of death, suicidal ideation, or a suicide attempt. To meet the criteria (1), these symptoms should represent a change from previous functioning and should occur most of the day.

Minor depression is similar to major depression in that patients experience depressed mood or anhedonia during the same two-week period. However, the patient's symptoms are fewer than the five items required to make a diagnosis of major depression [14]. Dysthymia is characterized by depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for at least 2 years [14]. In addition, at least two of the following symptoms should be present while the patient is depressed [1]: i) poor appetite or overeating; ii) low self-esteem; iii) insomnia or hypersomnia; iv) poor concentration or difficulty making decisions; v) low energy or fatigue; and vi) feelings of hopelessness. Patients with dysthymia typically have fewer symptoms (less than five) than is required to make a diagnosis of major depression [14].

Screening for depression

The diagnosis of depression is based on clinical findings. Several valid and reliable screening instruments are available for use in primary care [15-20]. The 9-item Patient Health Questionnaire (PHQ-9) [20] is an easy to use depression screening instrument. The PHQ-9 is a brief questionnaire that scores each of the 9 DSM-IV criteria for depression as "0" (not at all) to "3" (nearly every day). PHQ-9 score > or =10 have a sensitivity of 88% and a specificity of 88% for major depression. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe and severe depression, respectively [20]. The use of brief screening instruments to screen for depression in primary care patients is supported by the United States Preventive Services Task Force [21]. However, screening alone is not sufficient. It is important to have a system in place to confirm the diagnosis, offer guideline concordant treatment, and refer complex patients, or patients who do not respond to adequate dosage of two antidepressants.

Prevalence of depression in diabetes in individuals with diabetes

More than 300 years ago Dr. Thomas Willis, a British physician, made the observation that there was a relationship between diabetes and depression when he suggested that diabetes was the result of "sadness or long sorrow" [22]. Anderson and colleagues conducted a meta-analysis of 42 published studies that included 21,351 adults and found that the prevalence of major depression in people with diabetes was 11% and the prevalence of clinically relevant depression was 31% [23]. However, worldwide estimates of depression prevalence among individuals with diabetes appear to vary by diabetes type and among developed and developing nations. For example in the U.S., Li and colleagues examined data from the 2006 Behavioral Risk Factor Surveillance System (BRFSS), a standardized telephone survey of U.S. adults aged 18 and older and found that the age adjusted rate of depression was 8.3% (95% CI 7.3–9.3), ranging from a low of 2.0% to a high of 28.8% among the 50 states [24]. They also noted a 25-fold difference in the rates among racial/ethnic subgroups (lowest, 1.1% among Asians; highest, 27.8% among American Indians/Alaska Natives).

Li and colleagues also completed a second study using 2006 BRFSS data to estimate the prevalence of undiagnosed depression among individuals with diabetes [25]. In the second study, they found the adjusted and unadjusted prevalences of undiagnosed depression to be 8.75 and 9.2% respectively. Their secondary finding was that about 45% of all diabetes patients had undiagnosed depression [25]. Asghar and colleagues found evidence of depressive symptoms in 29% of male and 30.5% of female newly diagnosed diabetic patients in rural Bangladesh [26]. Similarly, Sotiropoulos and colleagues found that 33.4% of a cohort of Greek adults with type 2 diabetes reported

elevated depressive symptoms [27]. Zahid and colleagues found a more modest depression prevalence (14.7%) among patients with diabetes in a rural area in Pakistan [28]. However, Khamseh, Baradaran and Rajabali found major depression in 71.8% of a sample of 206 Iranian patients with type 1 and type 2 diabetes [29]. In a study of 143 patients with type 2 diabetes and 132 healthy controls in Bahrain, an island country with a high prevalence of type 2 diabetes, Almawi and colleagues found a higher proportion of type 2 diabetes patients in both the mild-moderate and severe-extremely severe depression categories [30]. In a bi-national study of more than 300 patients designed to examine the prevalence of depression in Hispanics of Mexican origin, Mier and colleagues found that the rate of depression among Hispanic patients was 39% in South Texas (USA) and 40.5% in Northeastern Mexico [31]. Elevated depressive symptoms have also been reported in African Americans residing in rural counties in Georgia (USA) [32] and urban primary clinics in East Baltimore, Maryland (USA) [33] .

In a systematic review designed to estimate the prevalence of clinically depressed patients with type 2 diabetes, Ali and colleagues found that the prevalence of depression was significantly higher among patients with type 2 diabetes (17.6%) than those without diabetes (9.8%) [34]. They also found that the prevalence among females with diabetes (23.8%) was higher than their male counterparts with diabetes (12.8%). Overall, studies have demonstrated that individuals with diabetes are more likely to have depression than in individuals who do not have diabetes. It should be noted however that the mechanisms linking these conditions are not entirely clear. For example, Mezuk and colleagues completed a review of studies from 1950 to 2007 of diabetes and depression to examine the bi-directional relationship between diabetes and type-2 diabetes [35]. The pooled relative risk for incident depression associated with baseline diabetes was 1.15 (95% CI 1.02-1.30) while the relative risk for incident diabetes associated with baseline depression was 1.60 (95% CI 1.37-1.88). In summary, depression was associated with a 60% increase of type 2 diabetes while type 2 diabetes was only associated with a moderate (15%) risk of depression. Additional research is needed to further delineate the relationship between these two comorbid conditions.

Causal pathways between depression and diabetes

Depression is associated with type 2 diabetes, however the direction of the relationship is unclear. For example the research by Knol and colleagues suggests that in addition to depression being a consequence of diabetes, depression may also be a risk factor for the onset of diabetes[36]. These findings among others suggest that there is strong evidence for a bidirectional relationship between diabetes and depression. This bidirectional relationship was confirmed by a recent study by Golden and colleagues in which they found that among individuals without elevated depressive symptoms at baseline, patients treated for diabetes had higher odds of developing depressive symptoms during the follow-up period [37]. In contrast, individuals with impaired fasting glucose and those with untreated diabetes had reduced risk of incident depressive symptoms. The authors found that these findings were comparable across race/ethnicity. Consequently, a bidirectional longitudinal association between type 2 diabetes and elevated depressive symptoms was observed [37].

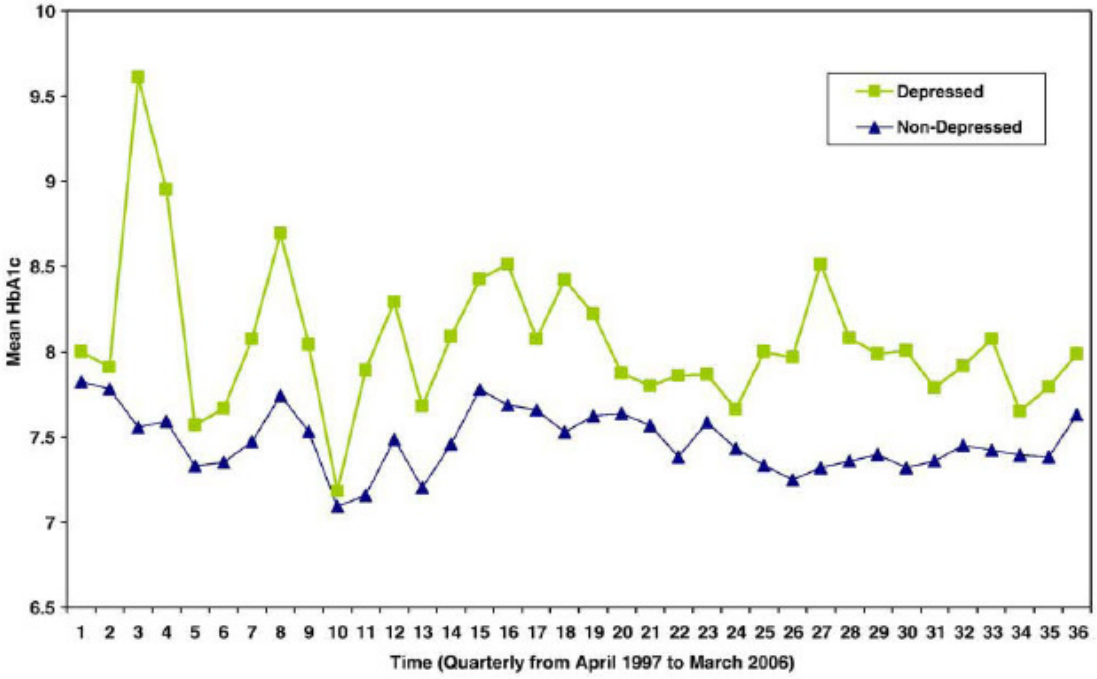
Two major hypotheses currently exist to explain the causal pathway between diabetes and depression. One hypothesis asserts that depression precedes type 2 diabetes (i.e. depression increases the risk of developing diabetes). Unfortunately, the mechanisms underlying the association between diabetes and depression are not clearly understood. In theory, the increased risk of type 2 diabetes in individuals with depression is believed to result from increased counter-regulatory hormone release and action, alterations in glucose transport function, and increased immunoinflammatory activation [38]. These physiologic alterations are thought to contribute to insulin resistance and beta islet cell dysfunction, which ultimately lead to the development of type 2 diabetes. The second hypothesis is that depression in people with both type 1 and type 2 diabetes results from

chronic psychosocial stressors of having a chronic medical condition [39]. This hypothesis is supported by at least two important studies. First, 8,870 participants from the first National Health and Nutrition Examination Survey Epidemiologic Follow-up Survey who were free of diabetes at baseline were assessed for depression and followed for 9 years [40]. Compared to those with no depressive symptoms at baseline, those with high or moderate depressive symptoms did not have significantly higher incidence of diabetes over the study period. Second, 1,586 older adults from the Rancho Bernardo study were screened for type 2 diabetes with a 75g oral glucose tolerance test and screened for depression with a modified Beck's Depression Inventory [41]. There was no evidence that depression was associated with incident diabetes, instead, the study showed that there was a 3.7-fold increased odds of depression in those with a prior diagnosis of diabetes.

Effect of depression on glycemic control and other self-care behaviors

There is substantial evidence that co-morbid depression among individuals with diabetes is associated with poor diabetes outcomes such as glycemic control. Lustman and colleagues completed a meta-analysis of 24 studies and found that depression was significantly associated with poor glycemic control in individuals with type 1 and type 2 diabetes [42]. The standard effect size was 0.17 (small to moderate) and was consistent (95% CE, 0.13-0.21). Similar effect sizes were noted for type 1 and type 2 diabetes but were larger when standardized interviews and diagnostic criteria were used rather than self-report questionnaire. Richardson and colleagues went a step further and assessed the longitudinal effects of depression on glycemic control [43]. They found that over four years of follow up there was a significant longitudinal relationship between depression and glycemic control and that depression was associated with persistently higher HbA1c levels over the time period (See Figure 1). Wagner and colleagues also found higher A1c and more diabetes complications in African Americans with higher depressive symptoms after controlling for confounders [44]. In this study, diabetes self-care did not fully account for the relationship between depression and A1c levels. Finally, Miranda and colleagues reported that variations in depressive mood below the level of clinical depression were associated with differences in glycemic control among patients with type 1 diabetes [45].

Figure 1 Comparison Of Unadjusted Mean Hba1c Over Time Among Depressed And Non-Depressed Adults With Diabetes



Adapted with permission from Richardson LK, Egede LE, Mueller M, et al., *Gen Hosp Psychiatry.* 2008; 30(6):509-514

Glycemic control is only one among a number of appropriate self-care behaviors that are critical to good diabetes care and consequently short and long term outcomes. Clinical management guidelines emphasize the importance of medication adherence, physical activity, diet and self-monitoring of blood glucose [46]. Gonzalez and colleagues proposed that the presence of depressive symptoms are good predictors of poor adherence to self-care particularly in adherence to medications and diet and exercise regimens [47]. Therefore, interventions should simultaneously address depression and self-care skills to achieve optimal diabetes outcomes. A systematic review of treatment adherence among individuals with diabetes and depression indicated that there was a significant relationship between depression and treatment non-adherence [48]. Effects sizes in the study were largest for medical appointments and composite measures of self-care (r=0.31, 0.29). Similarly, a systematic review of studies of medication adherence found that many patients did not adhere properly to diabetic medications [49]. A second review of self-management behaviors also concluded that co-morbid depression in individuals with diabetes is associated with not only decreased adherence to medications but also decreased adherence to dietary recommendations [46]. Co-morbid depression among individuals with diabetes generally has a negative impact on patient-initiated activities such as less physical activity, unhealthy diet and lower adherence to oral medications (hypoglycemic, antihypertensive, and lipid lowering) [50]. Gonzalez and colleagues found that after controlling for relevant covariates, patients with major depression reported significantly fewer days of adherence to diet, exercise and glucose self-monitoring self-management strategies and a 2.3 fold greater odds of missing medication doses compared to other respondents [51]. It is possible that patient attitudes play a critical role in self-care behaviors and depression impairs good self-care practices by influencing good self-care practices and perceived self control [52]. Table 1 shows the association between depression and diabetes self-care behaviors.

Table 1 Relationship of Depression and Diabetes Self-care Behaviors

Self-Care Activities (past 7 days)	Major Depression	No Major Depression	Odds ratio	95% CI
Healthy eating once weekly or less	17.2%	8.8%	2.1	1.59 - 2.72
5 servings of fruits and vegetables once weekly or less	32.4%	21.1%	1.8	1.43 - 2.17
High fat foods ≥6 times weekly	15.5%	11.9%	1.3	1.01 - 1.73
Physical activity (≥30 min) once weekly or less	44.1%	27.3%	1.9	1.53 - 2.27
Specific exercise session once weekly or less	62.1%	45.8%	1.7	1.43 - 2.12
Smoking: Yes	16.1%	7.7%	1.9	1.42 - 2.51

Adapted with permission from Lin EH, Katon W, Von Korff M, et al, *Diabetes Care.* 2004; 27(9):2154-2160

Effect of depression on risk for diabetes complications

Diabetes complications are also greater among individuals with depression. In a meta-analysis of 27 studies including adults with type 1 and type 2 diabetes, de Groot and colleagues found significantly greater diabetes complications including: diabetic retinopathy, nephropathy, neuropathy, microvascular complications and sexual dysfunction [53]. Effect sizes were in the small to moderate range (0.17 to 0.32). Clouse and colleagues found that the onset and prevalence of coronary heart disease was affected in women with diabetes who were depressed [54]. Studies have also shown a negative relationship between depression and poor glycemic control and diabetes complications in ethnic minorities. In a six-year longitudinal study of depression in relationship to glycemic control as risk factor for diabetic retinopathy, Roy and colleagues found that depression was significantly associated with proliferative diabetic retinopathy in a cohort of approximately 500 African Americans with type 1 diabetes [55]. Worse glycemic control was also observed in depressed adults with diabetes in an American Indian community in Arizona (USA) [56] and among a cohort of Hispanic American patients residing in New York (USA) [57]. Similarly, results from the Hispanic Established Population for Epidemiologic Study of Elderly (EPESE) Survey concluded that depression in individuals with diabetes was significantly associated with increased microvascular and macrovascular complications in elderly Mexican Americans with type 2 diabetes [58].

Effect of depression on disability, work productivity and quality of life in individuals with diabetes

Diabetes and depression are common chronic conditions that are significantly associated with increased odds of disability [59]. In a study of more than 30,000 adults ≥ 18 years of age from the National Health Interview Survey (NHIS) conducted in the United States, Egede found that the odds of functional disability was more than seven-fold greater among adults with diabetes and major depression compared to adults without diabetes and depression [59]. Results from the Hispanic Established Population for Epidemiologic Study of Elderly (EPESE) Survey also demonstrated greater disability among depressed adults with diabetes [58]. Patients with diabetes and coexisting depression had a 4.1-fold increase odds of disability compared to a 1.7-fold increase among adults with diabetes only and a 1.3-fold increase among adults with depression alone. Decreased work productivity has also been associated with the presence of depression in adults with

diabetes. In a second study, Egede found that adults with diabetes and depression were more likely to miss more than seven work days in any given year [60]. Erin and colleagues found that the presence of depression resulted in a significant deterioration in quality of life in individuals with diabetes [61]. In a second population-based US survey in 2004, lower health-related quality of life was observed in patients with diabetes and those at high risk for diabetes (3-5 diabetes-related risk factors) [62]. These findings suggest that the coexistence of diabetes and depression has a synergistic effect on the odds disability and in turn reduced work productivity and quality of life.

Effect of depression on healthcare utilization and costs in individuals with diabetes

Recent studies indicate increased healthcare utilization and healthcare costs among individuals with diabetes and coexisting depression. In a study of 55,972 adults with diabetes, Le and colleagues found that patient with diabetes and depression had higher diabetes-related medical costs (USD3,264) than patients with diabetes alone (USD1,297) [63]. They also found that depressed patients with diabetes had higher total medical costs (USD19,298) than patients without depression (USD4,819). Ciechanowski and colleagues found that individuals with diabetes and depression had a two-fold increase in healthcare costs compared to those who did not have depression [64]. In a third study, Finkelstein and colleagues found that U.S. Medicare beneficiaries with diabetes and major depression sought more treatment for more services, spent more time in inpatient facilities and incurred higher medical costs than adults with diabetes alone [65]. Nichols and colleagues found that in adjusted analyses, individuals with diabetes and minor depression used more ambulatory care visits and prescriptions than non-depressed adults even though depression alone was not associated with higher resource use [66]. Similar findings were reported in another study that used a U.S. nationally representative sample in which individuals with diabetes and depression had higher ambulatory care use and filled more prescriptions than their non-depressed counterparts [67]. In the same study, Egede and colleagues also found that among individuals with diabetes, total healthcare expenditures were 4.5 times greater among those who were depressed than those who were not depressed (See Tables 2 and 3). Studies of healthcare utilization and healthcare costs confirm that the coexistence of depression among individuals with diabetes is associated with greater healthcare service utilization and costs.

Table 2 Comparison of mean healthcare use among depressed and non-depressed individuals with diabetes, USA, 1996

	Depressed		Non-Depressed		
Utilization Category	**n**	**Mean Utilization**	**n**	**Mean Utilization**	**P***
Ambulatory Visits	85	12	708	7	0.0001
Emergency Department Visits	29	1	144	1	0.1624
Hospital In-patient Days	23	1	147	1	0.8983
No. of Prescription Medications	85	43	717	21	<0.0001

* P value for mean log 10-transformed utilization adjusted for age, gender, ace/ethnicity, health insurance and co-morbidity.

Adapted with permission from Egede LE, Zheng D, Simpson K, *Diabetes Care.* 2002; 25 (3):464-470

Table 3 Comparison of mean healthcare expenditures among depressed and non-depressed individuals with diabetes, USA 1996

	Depressed		Non-Depressed		
Expenditure Categories	**n**	**Mean Expenditures* (USD)**	**n**	**Mean Expenditures* (USD)**	**P** value**
Ambulatory Expenditures	85	920	708	666	0.1235
Emergency Department Expenditures	26	350	130	383	0.8524
Hospital In-patient Expenditures	23	10,082	147	7,648	0.1802
Prescription Medication Expenditures	85	1,392	717	666	<0.0001
Other Medical Expenditures	35	188	239	211	0.7883
Total Expenditure	**85**	**247,492,008**	**732**	**55,406,559**	**<0.0001**

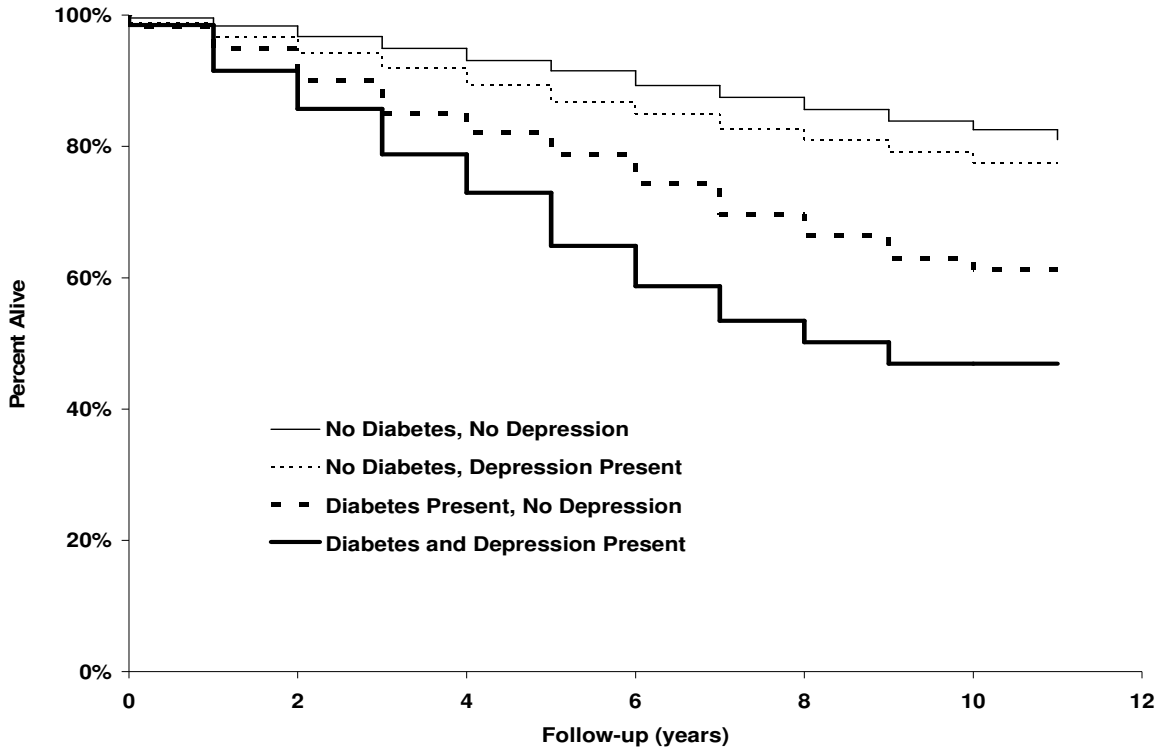
*Expenditures are adjusted for inflation with the Consumer Price Index to reflect August 2001 dollars.
** P value for mean log 10-transformed expenditures adjusted for age, gender, race/ethnicity, health insurance, and co-morbidity.

Adapted with permission from Egede LE, Zheng D, Simpson K, *Diabetes Care.* 2002; 25 (3):464-470

Effect of depression on mortality in individuals with diabetes

Recent studies have shown that coexisting depression increases the risk of death among people with diabetes [68-70]. In a study of 10,704 Medicare beneficiaries in the United States, Katon and colleagues reported that beneficiaries with diabetes co-morbid depression had a 36% to 38% increased risk for all-cause mortality over a two-year period [69]. In a study using the first National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study, results indicated that diabetic individuals with depression had a 54% greater mortality than those without depression [68]. In a third study of 10,025 patients from the NHANES I Epidemiologic Follow-up Study who were followed for eight years, Egede and colleagues found that hazard rates for all-cause mortality for individuals who had diabetes and depression were 2.50 (95% CI, 2.04-3.08) compared to those without diabetes or depression [70]. In that study, the authors concluded that the coexistence of diabetes and depression is associated with significantly higher risk of death and this risk is beyond that due to having either diabetes or depression alone (See Figure 2).

Figure 2 Effect of Depression on All-Cause Mortality in Patients with Diabetes



Adapted with permission from Egede LE, Nietert PJ, Zheng D, *Diabetes Care.* 2005;28(6):1339-1345

Effectiveness of treating depression in individuals with diabetes

Evidence suggests that recognition and treatment for depression is less than ideal and particularly in primary care settings where most people with diabetes receive care [71].

Despite increased efforts to identify and manage depression among people with diabetes, several important questions remain. First, does recognition of depression improve patient outcomes? Second, is recognition of depression based on a single visit appropriate? Third, what is a reasonable timeframe to determine failure of recognition? The answers to each of these questions remain generally unanswered therefore significant gaps currently remain in literature regarding the reliability of depression recognition.

There is an emerging evidence literature regarding the efficacy and cost-effectiveness of treatments for depression. Both pharmacological and non-pharmacological approaches to treatment of depression have been considered. At least three major pharmacological clinical trials have been conducted to determine the effectiveness of treatment of depression on depression and diabetes outcomes. In the first study, 68 patients with diabetes and depression were randomly assigned to eight weeks of treatment with nortriptyline to achieve plasma levels of 50-150ng/ml [72]. Patients demonstrated significant improvements in mood however significant improvements were not observed in glycemic control. In the second study, 60 subjects with diabetes and depression were randomly assigned to treatment with fluoxetine (up to 40mg per day) [73]. Treatment with fluoxetine was associated with significant improvement in mood but not glycemic control. A third study by Williams and colleagues was designed to assess whether enhancing treatment for depression improved mood and glycemic control in 417 elderly subjects (age ≥60 years) with diabetes and depression [74]. Patients were treated with antidepressants or psychotherapy; a care manager offered education, problem solving and assistance with medication management; and patients were followed for 12 months. Collaborative care for depression in the elderly improved mood and function but had no significant effect on glycemic control.

A systematic review of the efficacy of non-pharmacological treatments for depression concluded that depression-focused interventions reduce depressive symptoms in patients with diabetes, although they might not be associated with optimal diabetes outcomes (e.g glycemic control) [75]. At least three studies have examined whether psychotherapy alone or in combination with pharmacotherapy improve depression and diabetes outcomes. In the first study, 51 subjects with diabetes and depression were randomized to cognitive behavioral therapy (CBT) plus diabetes education vs. diabetes education alone [76]. CBT was associated with significant improvements in both mood and glycemic control. The second study randomized 329 patients with diabetes and depression to a case management intervention or usual care to determine whether enhancing the quality of depression care improved depression and diabetes outcomes [77]. The collaborative model of care for depression improved depression care and outcomes but did not have significant effects on glycemic control. The third study was designed to test the effectiveness of 6-month and 12-month follow-up of CBT compared to blood glucose awareness training (CGAT) in patients with type 1 diabetes [78]. Snoek and colleagues found that both interventions resulted in lower depressive symptoms up to 12-months but only the CBT was effective in lower HBA1c in patients with high baseline depression scores.

Finally, the most recent comprehensive review of published randomized controlled trials of treatment of depression among individuals with diabetes by Petrak and Herpertz concluded that good scientific evidence exists that suggests that treatments for depression in patients with diabetes are effective [79]. Conclusions of the review indicated that treatments for depression in patients with diabetes can include: antidepressants, psychotherapy or combination therapies emphasizes medications and

psychotherapy. Unfortunately, the findings of the review also concluded that neither led to significantly better outcomes.

Cost of treating depression in individuals with diabetes

Studies of the economics of treatments of depressed individuals with diabetes have yielded positive results. A recent study of the cost-effectiveness of treatment of depression among individuals with diabetes by Simon and colleagues concluded that systematic depression treatment significantly increased time free of depression resulting in an economic benefit from the perspective of the healthplan [80]. Patients who received the systematic depression treatment accumulated a mean of 61 additional days free of depression (95% CI, 11 to 82 days) and had on average USD314 less costs associated with outpatient services. The net economic benefit was USD952 per treated patient when each day free of depression was valued at USD10 [80]. Similarly, patients participating in at least one clinical trial improved on measures of depression outcomes while also experiencing reduced medical costs. Katon and colleagues completed the Pathways depression intervention program as a comparison to usual care and found that patients in the intervention arm of the study experienced improved depression outcomes and reduced 5-year mean costs of USD3,907 compared to patients in the usual source of care arm [81]. In summary, these studies suggest that treatment of depression in people with diabetes is both efficacious and cost-effective and can result in improved overall diabetes outcomes.

Challenges and future directions for treatment of depression in individuals with diabetes

Most diabetic patients with depression are treated in primary care settings [4]. However, studies suggest that consistent recognition and treatment of depression is less than optimal in primary care settings [71]. One barrier to early recognition and treatment of depression among individuals with diabetes is the difficulty in separating the symptoms of depression from the symptoms of poor management of diabetes. For example, fatigue, gain or loss of weight, change in appetite, and sleep disturbances are common symptoms of both depression and poor diabetes management. The difficulties of distinguishing diabetes-related symptoms from depression were highlighted in a recent study which showed that the depression-diabetes symptom association is stronger than the association of diabetes symptoms with measures of glycemic control and diabetes complications [82]. Ludman and colleagues studied patients with major depression and found significantly more diabetes symptoms and that the overall number of diabetes symptoms was highly correlated with the number of depressive symptoms (See Table 4). Similarly, in a targeted screening study of 246 patients with high-risk profile for diabetes, Adriaanse and colleagues found that diabetic patients exhibited more symptoms of hyperglycemia and fatigue in the first year following diagnosis of type 2 diabetes than those patients who were not diagnosed with diabetes [83]. They concluded that symptom distress is associated with increased likelihood of negative mood for both patients with and without diabetes.

Table 4 Relationship of Major Depression to Diabetes Symptoms Adjusted for Complications and Glycohemoglobin Level

Diabetes Symptom	Major Depression	No Major Depression	Odds ratio	95% CI
Cold Hands and feet	49.4%	32.4%	1.93	1.57 - 2.38
Numbness in hands or feet	51.3%	32.6%	1.98	1.61 - 2.43
Pain in hands or feet	46.0%	25.2%	2.23	1.81 - 2.75
Polyuria	54.5%	33.7%	2.24	1.82 - 2.75
Excessive hunger	44.7%	20.3%	2.66	2.16 - 3.28
Abnormal thirst	46.2%	16.9%	3.30	2.67 - 4.08
Shakiness	39.2%	14.0%	3.33	2.66 - 4.17
Blurred vision	38.2%	14.2%	3.42	2.74 - 4.27
Feeling faint	10.9%	2.7%	4.00	2.74 - 5.86
Daytime sleepiness	84.4%	52.3%	4.96	3.79 - 6.48

Adapted with permission from Ludman EJ, Katon W, Russo J, et al, *Gen Hosp Psychiatry.* 2004; 26(6):430-436

Unfortunately, the challenges of treating individuals with diabetes and depression are influenced by both patient-related and healthcare system-related factors. Patient-related factors include stigma and negative perceptions of any aspect of mental illness such as depression. Consequently, patients may not acknowledge their depression or their lack of adherence to treatment recommendations as these may reflect personal failure. In addition, financial constraints, side effects of antidepressants, and implication of a mental health diagnosis on employment and insurability are among a host of other patient-related factors. Similarly, healthcare provider and healthcare systems may provide additional barriers resulting from poor provider knowledge of evidence-based guidelines, reimbursement issues associated with mental health diagnoses in primary care settings, insufficient referral networks in rural and suburban communities and negative perceptions of the time necessary to deal with depression [84]. Further, healthcare systems are burdened by fragmented care between general health and mental health services and the long standing practice of packaging mental health services as a "carve-out" program also reduce the overall effectiveness of care [4]. Unfortunately, services for mental health and substance use conditions have been separated from services for general medical conditions. Compounding this issue, many patients do not have adequate coverage for mental health conditions because healthcare payers have typically sold mental health coverage as separate products to employers and managed care programs. Together, these patient-related and healthcare system-related factors have limited the effectiveness of treatments for depression and decreased the chances of patients with diabetes and depression receiving optimal quality care.

Practice guidelines from the International Diabetes Federation indicate that because patients with diabetes are more likely affected to depression, periodic assessment and monitoring of depression and other mental health conditions is required in the management of patients with diabetes [85]. These guidelines also note that detection in brief encounters are problematic, and as such diabetes health professionals require basic training in identification and management of depression in patients with diabetes [85]. Additionally, there is a need for adequate communication/interview skills, motivational techniques and counseling skills for health professionals treating individuals with diabetes. Further, collaboration among mental health specialists with an interest in diabetes could facilitate optimal outcomes. Therefore, effective management of patients with diabetes and depression requires collaborative efforts between a number of healthcare disciplines including: primary care, endocrinology, psychiatry, psychology, nursing, pharmacy, and allied health professions. Unfortunately, in most clinical settings,

patient care is fragmented and requires referral to practitioners in the different disciplines, who in most cases are located at a distance from each other. Fragmented clinical care subsequently creates substantial obstacles to achieving optimal clinical outcomes for patients. A coordinated approach to the provision of quality care to people with diabetes and coexisting depression is needed [4]. Coordinated clinical care could only occur in the context of extensive implementation of effective strategies to increase recognition of depression, adoption of effective interventions to provide guideline concordant care, and integration of performance measures for depression into diabetes clinical guidelines. Currently, recognition of depression among individuals with diabetes is suboptimal, therefore global approaches to establish coordinated, multifaceted interventions to improve early recognition of depression and early initiation of treatment for depression are required to reduce the worldwide burden of depression among individuals with diabetes.

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