

Is depression an independent risk factor for the onset of Type 2 diabetes mellitus?

Abstract

Depression is one of the most common mental illnesses characterized by loss of pleasure, whereas diabetes is a metabolic disorder which leads to high serum glucose levels. Current literature supports the development of depressive symptoms in patients with chronic illnesses including diabetes. However, depression as a potential risk factor for diabetes has attracted a lot of attention for clinicians and researchers. It has been hypothesized that both diabetes and depression may be bidirectional in nature, and each may exacerbate the symptoms or play an important role in the development of the other. The most common association between them is the diagnosis of depression in Type 1 or Type 2 diabetes. As the matter of fact, diabetes has been reported to double the risk of depression. In this review article, we have summarized various scientific studies to evaluate the potential of depression as a risk factor for diabetes. MEDLINE search identified various articles assessing this hypothesis. Our review of literature indicate some support for depression as a risk factor for Type 2 diabetes however more clinical studies need to be performed to clarify the contribution of depression as an independent risk factor for diabetes and to check the diabetes epidemic from escalating at a higher rate.

Key words:

Diabetes, major depressive disorder, risk factors

Introduction

Major depressive disorder (MDD) is one of the most common mental illnesses in the USA affecting nearly 6.7% of the adult population.^[1] MDD is characterized by symptoms of a depressed mood and/or a loss of pleasure. Everyone has likely experienced symptoms of depression at some point in their lives. However, MDD also known as clinical depression occurs when the depressive symptoms are persistent and have a significant affect on the patient's social or occupational life or other important areas of their life.^[2] The Diagnostic and Statistical Manual of Mental Disorders Vth Edition is used to diagnose MDD. In addition to the required symptoms of a depressed mood and/or a loss of pleasure, patients may also present with symptoms such as changes in appetite, feelings of guilt or worthlessness, psychomotor agitation or retardation, fatigue, cognitive

dysfunction, and suicidal ideation.^[3] The etiology of MDD is considered multifactorial. Contributing causes include genetics, environmental factors, and neurochemical influences. The most widely accepted theory on the pathophysiology of MDD is the monoamine hypothesis, which contributes MDD to an imbalance of serotonin, dopamine, and/or norepinephrine. While MDD may occur in anyone, its prevalence is more common in women,

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persons 45–64 years of age, minorities, people previously married, unemployed, and person without health insurance coverage.^[1]

Diabetes is a metabolic condition in which the body either no longer produces insulin or is resistant to insulin both of which may result in high glucose levels in patients with the disease.^[4] The prevalence and the incidence of diabetes have increased in recent years. In 2012, 20.9 million Americans or 6.9% of the population had diabetes. The incidence is expected to increase to 9% by the year 2025.^[5,6] There are two types of diabetes, Type 1 and Type 2. Type 1 diabetes, previously known as juvenile diabetes, is the least common of the two making up approximately 5% of cases. It is first seen most commonly in children or young adults. It is the result of the inability of the pancreatic beta cells to produce insulin. Type 2 diabetes also known as insulin resistance is the most common of the two types of diabetes. It is secondary to the body's inability to utilize insulin efficiently, or the pancreas' inability to produce a sufficient amount of insulin to meet the needs of the body.^[4] Type 1 and Type 2 diabetes share many common symptoms such as frequent urination, increased thirst and hunger, extreme fatigue, blurred vision, and wounds that are slow to heal. In addition, patients with Type 1 diabetes may also experience weight loss, despite increased caloric consumption, whereas, the patient with Type 2 diabetes may also experience neuropathy or tingling, pain or numbness to the hands or feet.^[4]

The relationship between diabetes and depression may be bidirectional, they may each play a role in the development of the other or they each may exacerbate the symptoms of the other. The more common association between the occurrences is depression following a diagnosis of Type 1 or Type 2 diabetes. Diabetes has been reported to double the risk of depression.^[7] Patients with both diabetes and depression may also have poorer outcomes. These comorbidities are associated with poor metabolic control, a decreased quality of life and increased morbidity and mortality. A population-based study in patients diagnosed with diabetes and depression conducted by Lin *et al.* indicated that patients with depression are more likely to lack diabetes self-care activities (diet, exercise, nonsmoking, glucose monitoring, and foot checks) than patients with diabetes but without depression.^[8] Diabetic patients with depression are less adherent to their oral medications when compared to diabetic patients without depression even when there are no differences in preventative services and diabetes monitoring between diabetic patients with or without depression.^[8]

Mechanism of Correlation and Risk Factors

The causal relationship between diabetes and depression is unclear.^[9] There are two major hypotheses to explain

the relationship between diabetes and depression. One hypothesis states that depression may be secondary to the stress of having a chronic medical condition (i.e., diabetes Type 1 or 2) and not to the disease itself. The other hypothesis states that diabetes is secondary to the development of depression. This risk may be a result of (1) increase in release and action of counter-regulatory hormones such as catecholamines, glucocorticoids, growth hormones and glucagon that counteract the hypoglycemic effects of insulin by elevating the blood glucose level, (2) alterations in the glucose transport system such as glucose transporter-1, glucosetransporter-3 and glucosetransporter-4, and (3) increase in immunoinflammatory activation i.e., secretion of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor- α and interferon- α . These developments lead to insulin resistance and dysfunction of beta islet cells.^[10-13] Depression may also serve as a risk factor for diabetes due to lifestyle habits associated with depression. These lifestyle habits may include poor health behaviors such as smoking, high-fat diet, and excessive alcohol intake, which all attribute to an increased risk of diabetes.^[8,14] Thus, while it is known that there is a relationship between depression and diabetes, the direction of the relationship remains unclear. There are three main phases of treatment for patients diagnosed with MDD: The acute phase, which lasts about 6–12 weeks, in which the goal is remission, the continuation phase, lasting 4–9 months after remission is achieved, in which the goal is to eliminate residual symptoms or prevent relapse, and the maintenance phase, lasting at least 12–36 months, in which the goal is to prevent recurrence. Antidepressants are the primary pharmacologic agents used to treat MDD. A number of different classes of medications are available for antidepressant therapy. Some of the drug classes of antidepressants such as the tricyclic antidepressants (TCAs) (amitriptyline [Elavil[®]]), monoamine oxidase inhibitors (MAO-Is) (phenelzine [Nardil[®]]), selective serotonin reuptake inhibitors (fluoxetine [Prozac[®]]), and serotonin-norepinephrine reuptake inhibitors (venlafaxine [Effexor[®]]) exhibit adverse effects such as weight gain which is one of the risk factors of developing Type 2 diabetes mellitus.^[15,16] In addition, TCAs have also been associated with insulin resistance which is one of the defects that leads to the development of Type 2 diabetes.^[17,18] Because of the weight gain associated with these antidepressants, patients experiencing depression are predisposed to the development of Type 2 diabetes. Clearly, basic science supports the hypothesis that depression is a risk factor for Type 2 diabetes. Many clinical studies have been undertaken with the goal of investigating the theory that depression may lead to diabetes. This review attempts to summarize the literature data of such studies.

Data Sources and Study Selection

HSP and HY did the literature search. MEDLINE (1990-February 2015) was searched to identify relevant

studies. The search items were based on established terminology using Cochrane definitions where possible and were “diabetes,” “depression,” “insulin resistance,” “insulin sensitivity,” and “MDD.” The titles and/or abstracts were searched and reviewed to exclude any clearly irrelevant studies. The full texts of the relevant studies were then retrieved and read in full by two authors HSP and HY independently to determine whether the studies met inclusion criteria. The reference lists of studies that were included in the review article were checked for additional publications that might have been missed in our searches.

Criteria for Inclusion into the Review

Abstracts were read to gather information regarding the studies. The full article was only retrieved and read if the study met all of the following criteria: (a) Sample consisted of adults (≥ 18 years of age); (b) pre- and post-depression and diabetes or lack thereof was determined; (c) and positive or negative association between depression as risk factor for diabetes was reported.

Clinical Studies

Table 1 provides a summary of key clinical studies evaluating depression as a risk factor for diabetes.

A population-based study was conducted by Eaton *et al.* with an aim to evaluate the relation between the onsets of diabetes in patients diagnosed with depression.^[19] In this study, they interviewed 3481 patients in 1981. At the end of 13 years 847 patients died, 437 could not be located as they moved, and 300 refused to participate. By the end of 1996, around 1897 patients completed the interview. Among these 1897 patients, 103 patients were not at risk and 79 patients were missing which left them with 1715 at risk patients. Among 1715 at risk patients, 89 new cases of diabetes were recorded (5.2%). The incidence rate of diabetes was slightly higher in women as compared to men. The authors concluded that only MDD is associated with Type 2 diabetes after taking into consideration the sex, age, race, and body mass index (BMI) of the patients. This study had some severe limitations as they did not consider sad mood or depressed mood as the diagnostic criteria for MDD. Moreover, they also relied on patient self-reported diabetes data at the baseline and during follow-up. Other factors which can contribute to diabetes such as lack of physical exercise, family history, smoking, alcohol, and other chronic disease were also not considered.

In contrast, a study by Kawakami *et al.*, observed that patients with both moderate and severe depressive symptoms are at risk for Type 2 diabetes.^[20] This study lasted 8 years and was conducted on 2764 male employees of an electrical company in Japan. The incidence of diabetes was rigorously monitored via annual screening. During

the 8 long years, 41 subjects developed diabetes, but none of them developed insulin dependent diabetes. After controlling the other known risk factors such as age, BMI, smoking, and alcohol, it was concluded that patients who had moderate to severe levels of depressive symptoms are at 2.3 times higher risk for Type 2 diabetes as compared to nondepressed patients. However, one major limitation of the study was that the baseline diabetes and depression data was patient self-reported. Lack of female subjects was another limitation of this study.

Similarly, Carnethon *et al.* conducted a study lasting 21 years intended to predict incidental diabetes in patients with the symptoms of depression.^[21] This was a large study wherein 6190 patients were monitored for incidental diabetes. The depression symptoms in these patients were measured using general well-being depression subscale and were categorized to high, intermediate and low symptoms. It was observed that the incidental diabetes was highest among the patients with high number of depressive symptoms (7.3/1000 person-years), however, it did not differ between those who were categorized with having low (3.4/1000 person years) to intermediate (3.6/1000 person years) symptoms. Moreover, the educational background was reported to play an important role in the development of diabetes in depressed patients. It was observed that depressive symptoms had no impact on patients with at least high school education. However, this study is marred with a lot of limitations. Baseline and incident diabetes were largely based on patient self-report and annual glucose screening, and other clinical tests were not conducted.

Alternatively, Brown *et al.* tried to assess the history of previous depression in diabetic patients as compared to those without diabetes.^[22] Subjects were chosen from the administrative database of Saskatchewan health. Type 2 diabetes was identified using the diagnostic code and prescription record of the individual and depression was determined using the diagnostic code and antidepressant medication. For every case subject, two nondiabetic subjects were randomly selected, as controls, from the population set during the same index year. Like others, this study demonstrated a strong correlation between depression and Type 2 diabetes. They observed that individuals with newly diagnosed diabetes were 3 times more likely to have a history of depression as compared to nondiabetic patients. Statistically, they found that 1622 of 33,257 (4.9%) patients of a newly diagnosed case of diabetes were 30% more likely to have a history of depression as compared of 2279 (of 59,420) case of people without diabetes. Authors also observed that the increased risk remained even after controlling for sex and the number of physician visits but was limited to the age of 20–50 years. Limitations of this study were the use of administrative data, lack of clinical data, and the potential for undiagnosed diabetes in the subjects. Another limitation was the potential for surveillance bias as a depressed patient

Table 1: Diabetes and depression summary of literature studies

Authors (year published)	Study design/methods	Study population (number and type of patients)	Statistical design and strength	Outcomes measured (results)	Comments (limitations)
Eaton <i>et al.</i> (1996)	Population based prospective	1715 East Baltimore residents	Controlled for age, sex, race and socioeconomic status; also examined the degree of depression; large sample size; long follow-up time	Major depressive disorder is associated with Type 2 diabetes	Patient self-reported diagnosis; some confounders not controlled
Kawakami <i>et al.</i> (1999)	Prospective cohort	2764 male employees of an electrical company in Japan	Medical records/exam were used for depression and diabetes/not self-reported; family history of diabetes were controlled; also controlled for age, education, occupation, work shift, obesity, physical activity, smoking, alcohol, chronic medical conditions Survival analysis was used to use time to develop diabetes	Moderate to severe levels of depressive symptoms are at 2.3 times higher risk for Type 2 diabetes	Only male respondents; only employees of one electric company; results cannot be generalized
Carnethon <i>et al.</i> (2003)	Population based longitudinal	6190 residents of US (2858 men and 3332 women)	Long follow-up time (21 years); number of depressive symptoms (degree); examined mediating factors/interaction: age, race, gender, behavior, education, survival analysis used to consider time	Incidental diabetes was highest among the patients with high number of depressive symptoms	Diabetes were from death certificate, records and self-report (various sources); Type 1 and 2 diabetes were mixed
Brown <i>et al.</i> (2005)	Nested case-control	92,677 residents of Saskatchewan > 20 years old	Controlled for age; sex and number of physician visits; based on medical records	Patients diagnosed with diabetes were 3 times more likely to have a history of depression as compared to nondiabetic patients	Case-control study (not as strong as cohort); short follow-up time (7 years), use of administrative data, lack of clinical data, and potential for undiagnosed diabetes and surveillance bias
Carnethon <i>et al.</i> (2007)	Prospective population based cohort	4681 US residents > 65 years old	Controlled for age, race, sex, marital status, education, physical activity, smoking, alcohol, BMI, CRP, 4 different locations; 10 years follow-up; depression was measured directly (not based on memory); diabetes also measured in glucose level; survival analysis-time included	Depressive symptoms and increases in depressive symptoms over time are associated with increase in incidental diabetes	Only 65 or older diabetes is based on medication inventory
Golden <i>et al.</i> (2008)	Multicenter, longitudinal observational	10,048 ethnically diverse US men and women aged between 45-84 years	Allow examining racial differences given the sample design; good generalizability to geographic locations and racial groups; wide age range (45-84); follow-up time is kind of long (4 years); controlled for sex, race, education, smoking, income, other medications, BMI, lipid, blood pressure, IL-6, CRP, and diet/nutrition; interactions were examined	Depression is associated with modest increase in risk for Type 2 diabetes. It also supports the bidirectional association between diabetes and depression	Patient self-report of depression and diabetes, the depressive symptoms were only assessed over short time duration at the first follow-up visit which may not be enough time to develop depressive symptoms
Mommersteeg <i>et al.</i> (2012)	Prospective cohort	9514 residents of UK	Long follow-up time period; controlled for age, sex, education, income; controlled for energy, health, activity Survival analysis	Association of incidental diabetes with psychological distress	Diabetes is self-reported Depression is not an independent factor after controlling for some other factors
Icks <i>et al.</i> (2013)	Population based prospective cohort	4814 patients in western Germany	Follow-up is 5 years (kind of long); wide age range (45-75); age, sex, physical exercise, smoking status, living with partner and education were controlled for. German sample, which increase our generalizability	Risk and rate of diabetes was not higher in either depressed or nondepressed cohorts	Misclassification of depressed patients and not analyzing many confounders. 5 years may not be an adequate follow-up period
Windle and Windle (2013)	Two-wave longitudinal		Both concurrent and prospective relationships were examined; long time period Controlled for age, education, BMI, alcohol use, cigarette use, anxiety disorder, stressful events	Recurrent MDD was a risk factor for CVD and diabetes	Results not generalizable, depression and diabetes were patient self-reported impacting misrepresentation and validity

BMI – Body mass index; CVD – Cardiovascular disease; MDD – Major depressive disorder; CRP – C-reactive protein; IL – Interleukin

is more likely to visit a physician, get clinical work-up and has a higher chance of getting diagnosed with diabetes as compared to a control subject.

Golden *et al.* conducted a longitudinal study over the period of 5 years in which they recruited ethnically diverse USA men and women both aged between 45 and 84 years of age.^[23] They used a score of either 16 or more as defined by Center for Epidemiologic studies Depression Scale (CES-D) or the use of antidepressant, or both to identify elevated depressive symptoms. 5201 patients without diabetes were included at the baseline and estimated risk for incidental diabetes was measured. Furthermore, they analyzed 4847 patients with Type 2 diabetes without depressive symptoms. Results showed that the incidental Type 2 diabetes was 4.0/1000 patient years higher for those with depressive symptoms as compared to those without. Moreover, the risk incident diabetes increased with increase in CES-D score. In the analysis of the incidence of Type 2 diabetes causing depressive symptoms, they found that depressive symptoms were higher for patients who are being treated for Type 2 diabetes compared to those who are untreated. This study suggests that depression is associated with a modest increase in risk for Type 2 diabetes. It also supports the bidirectional association between diabetes and depression. The study utilized a large sample size from across the USA which gives it good external validity for the USA population. The limitations of the study were that the patients at baseline were selected based on the absence of coronary heart disease which is in turn associated with depressive symptoms. Depression analysis was based on CES-D method that relies mainly on patient self-report and is not official test for clinical depression. Furthermore, the depressive symptoms were only assessed over short time duration at the first follow-up visit which may not be enough time to develop depressive symptoms. The nature of the study is observational and hence it is difficult to establish cause and effect.

Carnethon *et al.* reported the age-related correlation of depression and diabetes.^[24] This study suggests that depressive symptoms and increases in depressive symptoms over time are associated with an increase in incidental diabetes in adults older than 65 years. This study involved the participants from cardiovascular health study who completed CES-D annually from 1989 to 1999. Diagnosis of diabetes based on initiation of hypoglycemic agents or insulin and not on clinical measurement is a major limitation of this study as it can lead to misclassification. Furthermore, CES-D score was used to assess depression that relies on patient self-report.

Mommersteeg *et al.* conducted an observational cohort study over a period of 18 years with 9514 participants.^[25] The results show an association of incidental diabetes with psychological distress. The study was done over a very long

period which means there was adequate time to see events in the study population. Diabetes and psychological distress were self-reported in this study which could have led to some reporting bias. The nature of the study design limits establishing cause and effect relationship.

Icks *et al.* conducted a population-based prospective cohort study in 4814 patients in Western Germany.^[26] The baseline data was gathered in year 2000 and 2003 and follow-up was conducted in 2005 and 2008. Subjects were either depressed or not depressed, and the end point of this study was to find the number of people who develop diabetes in both groups. The results of the study indicated that the risk of diabetes was not higher in either group and that the rate of developing diabetes was similar in both groups. The strength of this study was a low rate of follow-up losses and using blood glucose test to assess diabetes. Limitations included misclassification of depressed patients and not analyzing confounders such as marital status, physical activity, history and severity of depression, and emotional stress. Also, diabetes is a very slow developing disease and it is unclear if 5 years is an adequate follow-up period.

Windle and Windle conducted a longitudinal study in a cohort of middle-aged, white women to investigate the effect of MDD on cardiovascular disease (CVD) and diabetes.^[27] This study suggested that after controlling for age, educational level, tobacco use, alcohol use, and BMI, recurrent MDD was a risk factor for CVD and diabetes. The limitations of this study were that the results cannot be generalized to other ethnic groups or men because the sample consisted of primarily white, middle-aged women. Also, all data on depression and diabetes was patient self-reported which can lead to misrepresentation and impact validity.

Conclusions

Mechanism linking diabetes and depression and the causal direction of the association is not clear even though various research studies have been conducted to answer these questions. It has been established that clinical depression precedes incidental diabetes. However, what needs to be clarified is whether depression is an independent risk factor or is an accessory to other established risk factors such as family history, BMI, patient self-care behaviors, sedentary lifestyle, and poor diet for developing diabetes or accelerating the onset of diabetes in such patients. While more scientific data is being gathered, it seems prudent to be cognizant of the effect of some antidepressant drugs on the risk of diabetes. The use of some antidepressants, specifically, antidepressants those are associated with significant weight gain (i.e., TCAs, MAO-Is, mirtazapine) may contribute to the risk of diabetes. These results indicate that continued research is needed to clarify the contribution of depression as a risk factor for diabetes and to check the diabetes epidemic from escalating at a higher rate.

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Conflicts of interest

There are no conflicts of interest.

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