

# A Review of the Relationship Between Depression and Diabetes in Adults

## Is there a link?

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**OBJECTIVE** — To review the support for two hypotheses concerning the interrelationship between depression and diabetes and to identify areas in which more research is needed.

**RESEARCH DESIGN AND METHODS** — A review was conducted using primarily electronic databases. Articles relating to diabetes and depressive symptomatology, depressive disorder, and dysthymic disorder were selected. The study focuses mainly on adults with diabetes.

**RESULTS** — The initial onset of major depressive disorder (MDD) seems to be independent of the onset of type 2 diabetes, but results remain equivocal for type 1 diabetes. However, in both type 1 and type 2 diabetes, diabetes-related psychological and physiological processes may be involved in the higher recurrence and longer duration of MDD and depressive symptomatology.

**CONCLUSIONS** — The hypotheses that the initial occurrence of clinically significant depression, MDD, results from either biochemical changes directly due to type 2 diabetes or its treatment or from the psychosocial demands imposed by the illness or its treatment do not seem to be supported. MDD in diabetic individuals represents a multidetermined phenomenon resulting from interactions between biologic and psychosocial factors. This interaction may increase the probability of developing type 2 diabetes in otherwise healthy individuals.

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Empirical studies strongly suggest that depression is more prevalent among adults with diabetes than among the general population (1). To date, the reasons for the higher prevalence rates of depression in diabetic patients are not yet fully understood. The two dominant hypotheses concerning the initial occurrence or recurrence of clinically significant depression in individuals with diabetes are as follows: 1) it results from biochemical changes directly due to the

illness or its treatment and 2) it results from the psychosocial demands or psychological factors related to the illness or its treatment (2,3). The former hypothesis has also been referred to as a mood disorder due to a medical condition for which specific criteria have been formulated in *Diagnostic and Statistical Manual of Mental Disorders* (4th edition) (4). Both hypotheses are not mutually exclusive.

In recent years, an increasing number of studies have been published on dia-

betes and depression allowing new insights into the interrelationship between the two. We propose to integrate this literature to previous findings in light of the above-mentioned hypotheses and to identify areas in which more research is needed.

The first hypothesis states that the essential feature of a mood disorder due to a general medical condition, as defined by the American Psychiatric Association (APA), is “a prominent and persistent disturbance in mood that is judged to be due to the direct physiological effects of a general medical condition” (4). The determination of the presence of a mood disorder caused by a medical condition is a complex issue, especially in the absence of specific markers for depression. *Diagnostic and Statistical Manual of Mental Disorders* (4th edition), which is widely used in the mental health field, offers guidelines in this regard (4). These guidelines include 1) a temporal association between the onset, exacerbation, or remission of the general medical condition and the mood disorder; 2) features that are atypical of primary mood disorders (e.g., atypical age at onset or course, absence of family history, and equal sex distribution), and 3) evidence of a well-established or frequently found association between the general medical condition and the phenomenology of the mood disorder (e.g., the existence of a direct physiological mechanism or a lesion that relates the general medical condition and the mood disorder). We will use these guidelines as an organizing framework to review the evidence for hypothesis 1. It should be stressed that none of these considerations alone can prove an etiological relationship, but evidence in support of these postulates would increase the likelihood of such a relationship.

The second hypothesis specifies that depression results from the stresses and strains associated with having a chronic medical condition and its often debilitating consequences. Particularly, the role of diabetes-related cognitions, specifically illness intrusiveness, coping, and social support, has been the topic of numerous studies on depression in diabetes. We will examine

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**Abbreviations:** APA, American Psychiatric Association; MDD, major depressive disorder.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

the role of these factors for evidence of hypothesis 2.

For this study, the following electronic databases were explored to identify published literature: MEDLINE, Psychlit, Current Contents, SciSearch, and Social SciSearch through May 2000. The searches were supplemented by hand searches of key journals. Also, cross-referencing was used to search for relevant articles. From a reading of the titles (and abstracts when available), studies were selected as relating to diabetes and depression, depressive symptomatology, depressive disorder, and dysthymic disorder. With a few exceptions, only studies that included adults with diabetes were included. Further, only articles published in refereed journals in the English language were used. Throughout the article, we refer to diagnostic entities of depression (e.g., major depressive disorder [MDD]) in which researchers have used diagnostic interviews (semi-structured or structured) allowing such diagnosis to be made. When researchers relied only on self-report scales or rating scales to assess depression, the term depressive symptomatology is used.

## HYPOTHESIS 1

### **Depression in diabetes: A result of biochemical factors**

**Criterion 1: Presence of a temporal association between the onset, exacerbation, or remission of the general medical disorder and the mood disorder.** The literature suggests that the development of MDD precedes the diagnosis of type 2 diabetes by many years (5). In fact, recent findings have suggested an inverse temporal relationship, namely that MDD (6) and depressive symptomatology (7) may increase the risk for developing type 2 diabetes. In the case of type 1 diabetes, MDD typically follows its diagnosis (5,8). Kovacs et al. (8) reported that the first year of diabetes was the high-risk period for the initial onset for MDD. However, Lustman et al. (5) reported that the mean age of onset of MDD among individuals with type 1 diabetes was 22.1 years. This is slightly lower than the age of onset reported in the general population but later than the age at which type 1 diabetes is generally diagnosed (late childhood to early adolescence) (9). Given that for the majority of cases the initial onset of MDD seems to precede rather than follow the diagnosis of type 2 diabetes, it seems unlikely that diabetes is the cause of the initial onset of

MDD. Although the initial onset of MDD seems to follow the diagnosis of type 1 diabetes, it remains to be shown whether this temporal association is a causative one.

There is evidence that blood glucose levels of individuals with diabetes improve with remission of depression. Cases of hyperglycemia in individuals with type 1 or type 2 diabetes and symptoms of depression have suggested that hyperglycemia resolves with the treatment of clinical depression (given that these studies are earlier studies and the use of structured diagnostic interviews was not mentioned, it is not clear whether these treatments, either electroconvulsive therapy or antidepressant medication, were for cases having MDD or for lesser psychopathology) (10–14). More recently, Lustman et al. (15) extended these results to cognitive behavior therapy. Double-blind placebo and controlled treatment studies of MDD have also suggested a hypoglycemic effect of antidepressant medication (16,17). Possible mechanisms include changes in the effects of catecholamine levels and serotonin concentrations on glucose regulation (18). Unfortunately, changes in adherence to diabetes self-care activities were not measured in any of the above-mentioned studies, and therefore it remains possible that the found effects of the treatments of depression on metabolic control resulted from better adherence to self-care activities. Lustman et al. (19) found that nortriptyline had a hyperglycemic effect on glucose regulation, whereas mood improvement had a hypoglycemic effect. Weight change or compliance with a protocol for self-monitoring of blood glucose did not affect the results. However, mood improvement may have been related to better compliance with, for example, physical activity, which could explain the hypoglycemic effect. The hyperglycemic effect of nortriptyline remains unclear.

Thus, the underlying mechanisms involved are still not well understood, and the direction of the relationship between depression and metabolic control remains unclear. Most studies have focused on the effect of treatment of depression—either MDD or depressive symptomatology—on diabetes control. The examination of the effects of intensive treatment of diabetes (e.g., intensive insulin treatment) on MDD or depressive symptomatology would provide stronger evidence of an etiological relationship between clinically significant depression and diabetes control (20). So far, only one study (21) has addressed this

issue and found no significant change in depressed mood as a result of intensive insulin treatment. However, participants were asked to carry out repeated monitoring of blood glucose in addition to multiple insulin injections, increasing the burden of diabetes self-care, which may explain why mood levels did not improve. Also, participants in this study were not specifically selected for having MDD or depressive symptomatology, which reduces its relevance for the present discussion.

In sum, it is unlikely that the initial onset of MDD is the result of type 2 diabetes, but MDD may increase the risk of developing it. Results remain equivocal for type 1 diabetes. Control of diabetes improves with remission of MDD, but the underlying mechanisms remain unclear.

### **Criterion 2: Presence of features that are atypical of primary mood disorders.**

*Atypical course of the disease.* A few studies have been conducted to assess the course of MDD in individuals with diabetes, with most suggesting that depression has a higher recurrence rate (5,22) and longer duration (8). In a 5-year follow-up study, Lustman et al. (5) reported that 22 of 28 (79%) individuals with diabetes who had a lifetime history of mood disorders suffered from a mood disorder during that period, whereas only 2 of 20 (10%) individuals with diabetes without a history of psychiatric disorders developed a mood disorder during the same period. No difference was found between type 1 and type 2 diabetes. Similarly, in another 5-year follow-up study (22), 28 individuals with type 1 or type 2 diabetes participated in an 8-week controlled trial of nortriptyline for the treatment of MDD. After this 8-week trial, the primary care physicians were informed of the outcomes and advised to monitor for relapse and treat ongoing depression. It was found that recurrence or persistence of MDD occurred in 23 (92%) of the participants with an average of 4.8 MDD episodes over the 5-year follow-up period.

A 10-year prospective study was conducted to assess the course of MDD among 24 youths with type 1 diabetes and 30 psychiatric control subjects without a major systemic medical disorder (although this study was conducted among youths with diabetes, the assessment of the course of depression from the onset of type 1 diabetes explains its inclusion in this study) (8). Whereas similar rates of recovery from a first episode of MDD and of recurrence of a second episode were found in both indi-

viduals with diabetes and control subjects, episodes of MDD lasted longer among youths with diabetes. The results suggest that, although the duration of the MDD episodes is related to having type 1 diabetes, the recovery from the first episode and the overall risk of a second MDD episode are not.

Evidence for increased persistence of depressive symptomatology was also reported by Peyrot and Rubin (23) in 245 individuals with either type 1 and type 2 diabetes. Participants completed a self-report depression symptom inventory at the beginning and the end of a 1-week outpatient diabetes education program and at a 6-month follow-up. Although the presence of subclinical depression was found in only 13% of the participants at all three time points, 73% of those who were identified as having depressive symptomatology, both at the beginning and the end of the education program, also showed depressive symptoms at the follow-up. Contrary to Lustman et al. (5), who found no difference in the course of MDD between both types of diabetes, it was found that only individuals with type 2 diabetes who were non-insulin-treated were at risk for persistent depressive symptomatology. The results suggest that the risk factors associated with the course of depressive symptomatology may differ from those associated with MDD.

On the other hand, in a 2-year longitudinal community study, Wells et al. (24) found that the course of MDD did not differ significantly for depressed patients with and without a lifetime history of type 1 diabetes or hypertension. However, a number of methodological issues, such as the use of a self-report to diagnose illness and the inclusion of groups that were not mutually exclusive, limit the conclusions of their study.

In sum, although still insufficient, evidence is accumulating suggesting that MDD and depressive symptomatology have a higher recurrence rate and duration in diabetic patients.

*Presence of other atypical features (absence of family history and equal sex distribution).* A positive family history of MDD was found to be more common in individuals with diabetes suffering from MDD than in non-depressed diabetic subjects (27 vs. 3%) (25). This 27% rate is similar to that in depressed individuals who are otherwise medically well (26). Also, in Kovacs et al.'s (8) 10-year longitudinal study, MDD in mothers was found to be a specific risk fac-

tor for MDD in youths with type 1 diabetes as is in the general population (27).

Kovacs et al. (8) found no significant effect of sex on the initial occurrence of MDD but young women with diabetes were at a nine times greater risk for recurrent MDD than young men with diabetes. Lustman et al. (5) also reported a significantly higher prevalence of MDD in diabetic women than in diabetic men. However, their sample was comprised of a majority of women. Other researchers observed only a tendency for a sex differences (28–31), whereas Peyrot and Rubin (23) found that sex was related to transient but not persistent depressive symptomatology.

In summary, a positive family history is a typical feature of MDD, which is also found in individuals with diabetes. The effect of sex was found among youths with type 1 diabetes, but whether such an effect exists among depressed adults with diabetes remains unclear.

**Criterion 3: Evidence of a well-established or frequently encountered association between diabetes and the phenomenology of depression.** Several studies have reported common biologic substrates in diabetes and depression (32). For example, as in MDD, alterations in the activity of the HPA axis, such as increases in cortisol production, have been observed in individuals with diabetes (33,34). Also, alterations in the metabolism of neurotransmitters, particularly norepinephrine and serotonin, comparable with those found in MDD have been observed in streptozotocin-induced diabetes (35–38). Additional direct physiological mechanisms, which have particular relevance for type 2 diabetes, relate to the reduction of glucose use and to the increase of insulin resistance. Both mechanisms have been found in depressed individuals without diabetes (39–41).

The relationship between depression in individuals with diabetes and glycemic control is less obvious. For both types of diabetes, a significant relation between poorer glycemic control and MDD (5,19,22,42) or depressive symptomatology (43–46) has been reported. Other studies have not found a significant relation between glycemic control and MDD (47) or depressive symptomatology (23,48–53). Still others have found significantly worse glycemic control in individuals with type 1 diabetes and a lifetime history of MDD but not in those with type 2 diabetes (54).

Neurochemical changes associated with advancing diabetes may also contribute to

depression in individuals with diabetes (22). However, mixed findings have been reported regarding the relationship between diabetes complications and depression. Whereas the presence of complications in individuals with type 1 and type 2 diabetes was found to be related to depressive symptomatology (55,56) and MDD (57) in some studies, the number of complications that is associated with depression varied from at least two in one study (23) to more than three (52) or four in others (58). Still others found that only specific complications were associated with depression: both MDD and depressive symptomatology have been associated with the presence of neuropathy (15,59), whereas depressive symptomatology has also been linked to macrovascular disease (58). Finally, one study did not find a significant relationship between diabetes complications and depressive symptomatology (48).

Studies comparing the presence of diabetic complications in depressed and non-depressed individuals with diabetes did not find a significant difference (30,42). In a longitudinal study, psychiatrically well individuals with diabetes who developed new diabetic complications during a 5-year follow-up did not present disproportionate rates of mood disorders or of any other mental disorder (5).

The mere presence of disability may not be a sufficient factor to account for depressive symptomatology or MDD (60). As suggested by Lustman et al. (15), issues related to complications, the level of incapacity, and unique meanings that individuals attach to having complications may have to be addressed. In fact, the only known pathology that is etiologically linked to (late-onset) MDD is macro- and microvascular disease (61). Although the nature of the underlying mechanisms are not yet fully elucidated, there are data to support the notion that disruption of prefrontal systems or their modulating pathways by single lesions or by an accumulation of lesions exceeding a threshold are involved in "vascular depression" (62). Further, longitudinal studies have shown that it is MDD that increases the risk of complications in diabetes (63,64) rather than the opposite.

Overall, analysis using the APA (4) guidelines does not support the notion of a mood disorder caused by diabetes. If there was such a disorder, the empirical support would be stronger and clearer by now. However, biochemical factors may contribute to the recurrence and longer duration of MDD.

The evidence for the effect of MDD on diabetes is more persuasive, with longitudinal studies showing that MDD is associated with an increased risk of developing type 2 diabetes and diabetic complications.

## HYPOTHESIS 2

### **Depression: A result of the psychosocial demands imposed by diabetes**

Depression in diabetes may result from the increased strain of having a chronic medical condition rather than directly from the disease itself (65). A number of studies suggest that depressed mood is related to difficulties in adaptation to diabetic complications (66–70). Further, when the burden of diabetes increases (e.g., increasing number of complications), so does the probability of mood symptoms (23,58). Peyrot and Rubin (23) have pointed out that the emotional impact of a complication might be stronger immediately after its development. For example, some studies have reported that psychological distress increases during the first 2 years after diagnosis of proliferative retinopathy, regardless of its severity (68–70). It has also been found that fluctuating visual impairment affects psychological well-being more than severe but stable impairment (66). Further, acute complications compared with chronic complications are related to higher rates of depressive symptomatology (68). However, as Rubin (71) concluded in his study of psychotherapy in diabetes, “although many people may suffer psychological distress following a predictable crisis of diabetes, most accommodate over time, often quite rapidly and quite well.” Only for those with three or more complications was there an increased risk of developing depressive symptomatology.

The perceived disability associated with an illness (72) or being aware of having a chronic illness (73) may have more of an impact on one's life than the actual pathology. In an intriguing population-based study (73) among 1,586 men and women aged 50 years or older, prevalence rates of mild-to-severe depressive symptomatology were found to be 3.7 times higher among individuals with previously diagnosed diabetes who were aware of their condition (by medication use) ( $n = 93$ ) than among individuals not diagnosed and thus not aware of having diabetes ( $n = 209$ ) (by the World Health Organization's criteria including a glucose tolerance test) and individuals without diabetes who may have had other chronic conditions ( $n =$

1,284). No significant differences in the number of other chronic diseases (cancer, arthritis, hypertension, ulcers, and kidney disease) were found between the previously diagnosed and newly diagnosed groups. Unfortunately, the duration of diabetes in the individuals with previously diagnosed diabetes was not specified, nor was it known whether the participants in the previously diagnosed group had more complications than those in the undiagnosed group.

The relationship between disability and depressive symptomatology is likely to be mediated by psychosocial variables, such as illness intrusiveness, social support, and coping. The relation of these variables to diabetes is discussed below.

### **Perceptions of illness intrusiveness**

Many studies have shown that for a number of diseases, including diabetes, the relationship between disease variables (e.g., disability) and negative mood is mediated by perceived illness intrusiveness (74–78). These findings support a general model of the psychosocial impact of chronic physical illnesses, which has illness intrusiveness at its core (79,80). This research is also in line with that of Davis et al. (81) who showed that the social impact of diabetes (e.g., traveling, being active, having good relations, and keeping a preferred schedule) is associated with an increased risk of mortality, although causal relationships could not be inferred from this study.

### **Social support**

Whether the burden of illness will lead to depression may also depend on the level and quality of social support. For example, Beekman et al. (60) found that the association between chronic disease and depressive symptoms was weakened in the presence of higher levels of social support. For diabetes, significant relationships were found between general or diabetes-specific social support and depressive symptomatology (82) or psychosocial adjustment to diabetes, including emotional well-being (83). White et al. (83) postulated that poor health status limits the opportunity for the chronically ill to develop and maintain social relations, therefore contributing to emotional distress. Two studies in which health-related disruptions to social relations and activities were found to be related to lower levels of morale in adults with type 2 diabetes add further support to this hypothesis (84,85).

### **Coping**

Another variable that may mediate the relationship between illness and depression relates to a patient's coping skills (86). For example, White et al. (83) found that the individuals with diabetes who used palliative coping strategies, such as wishful thinking and behavioral efforts to escape or avoid problems, had poorer psychological adjustment. The authors postulate that when health deteriorates, sometimes in spite of all efforts to manage the disease, individuals may be overwhelmed and be more likely to use passive coping strategies. Cox et al. (87) speculated that because strict adherence does not guarantee good diabetes control or avoidance of complications, this is fertile ground for the development of learned helplessness and possibly subsequent depression for those who make painstaking efforts to strictly follow treatment recommendations. Whereas such hypotheses are interesting, to date, only a few studies have examined the link between depressive symptomatology and adherence (56) but none in the context of MDD. These studies indicate that more demanding regimens and lower levels of adherence are associated with depressive symptomatology.

Overall, very little research has been carried out on the role of psychosocial factors in diabetes and depression. The available empirical data appear to support, rather than contradict, the hypothesis that disease-specific psychological variables are associated with depressive symptomatology in individuals with diabetes. A number of studies suggest that such variables could mediate the relationship between diabetes status and depressive symptomatology. However, the cross-sectional nature of these studies precludes causal inferences. Also, because MDD has not been the topic of investigation in any of the studies, we cannot draw a conclusion as to whether the indirect link between diabetes status and depressive symptomatology also extends to MDD.

**CONCLUSIONS** — Research on the causes of depression in individuals with diabetes is progressing slowly, but some patterns are now beginning to emerge. First, with the possible exception of late-onset MDD, which is believed to result from micro- or macrovascular disease, the onset of MDD typically precedes the diagnosis of type 2 diabetes by many years. Therefore, it seems unlikely that the ini-

tial onset of MDD is caused by type 2 diabetes for the majority of cases. Findings, such as a positive family history of MDD and a sex distribution similar to that in depressed individuals without diabetes, also strengthen the notion that MDD in type 2 diabetes is similar to MDD in the general population. The hypotheses that the initial occurrence of clinically significant depression, or MDD, results from either biochemical changes directly due to type 2 diabetes or its treatment or from the psychosocial demands imposed by the illness or its treatment seems, therefore, are not supported. Rather, evidence is accumulating for the inverse hypothesis that the presence of MDD or depressive symptomatology increases the risk of developing type 2 diabetes and diabetes-related complications. Underlying factors may include the increase in insulin resistance and reduction of glucose uptake resulting from MDD. We may speculate that these metabolic changes contribute to the destabilization of a pre-existing precarious metabolic balance among individuals at risk for developing type 2 diabetes (88,89).

Findings regarding causality of MDD are less clear for type 1 diabetes. Given that the first episode of MDD typically follows the diagnosis of diabetes, the possibility still exists that MDD is a consequence of having type 1 diabetes. Longitudinal studies examining the effects of intensive insulin treatment on MDD while controlling for adherence to self-care activities could help to elucidate this issue. So far, evidence of a positive family history of MDD along with high rates of maternal depression in type 1 diabetes similar to those found in depressed nondiabetic individuals, seems to suggest that MDD in type 1 diabetes is similar to MDD in the general population.

As for subclinical levels of depression (depressive symptomatology), there is currently no evidence available to conclude whether high levels of depressive symptoms occur as a consequence of having type 1 or type 2 diabetes or that these symptoms are part of conditions independent of diabetes (e.g., MDD and dysthymia).

A second pattern of results suggests that, for both types of diabetes, the course of MDD or subclinical levels of depression is not independent of diabetes and its consequences. Although based on a limited number of studies, evidence is accumulating that MDD has a higher recurrence rate, and depressive episodes may last longer in individuals with type 1 or type 2 diabetes.

There is also some evidence of increased persistence of depressive symptomatology among non-insulin-treated individuals with type 2 diabetes. However, further studies are needed before any firm conclusions can be drawn.

Covariation between diabetes and depression is also suggested by studies showing improved diabetes control after remission of MDD. However, whether improvements in diabetes control after treatment for depression result from direct physiological changes (e.g., changes in the HPA axis and in metabolism of neurotransmitters, decreases in insulin resistance), improved adherence to diabetes self-care activities, or altered perceptions of diabetes and its ramifications remains to be determined. To date, some common biologic substrates of diabetes and depression have been identified, but no systematic relationships have been found between glycemic control and either MDD or depressive symptomatology. Methodological differences between studies such as the use of cross-sectional versus longitudinal designs, control for number and type of complications, control for frequency, and direction of self-care activities may account for these differences.

Whereas the number and type of diabetes complications have been found to affect mood, awareness of having diabetes and the perception of diabetes as disabling may be more related to depressive symptomatology than the complications per se. In this regard, illness intrusiveness, social support, and coping strategies may mediate the relationship between disease variables and depression. Unfortunately, given the cross-sectional nature of the studies examining these psychosocial factors, no conclusions regarding causal inferences can be drawn. Also, studies on the role of psychosocial factors in depression and diabetes were limited to self-reported depressive symptomatology rather than specifically targeting individuals with MDD. Longitudinal studies on the involvement of psychosocial factors in MDD in diabetes should have high research priority.

Overall, the literature suggests that the course of MDD in individuals with diabetes is not causally independent of diabetes. More than likely, MDD in individuals with diabetes represents a complex phenomenon resulting from interactions between genetic, biologic, and psychosocial factors, which may account for the recurrence and longer duration of MDD. More recent findings suggesting that reciprocal interactions between

MDD and diabetes are likely because MDD and depressive symptomatology may increase the risk for onset of type 2 diabetes and the likelihood of developing diabetic complications, which further add to the complexity of the phenomenon.

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