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Recent Advances in Understanding Depression in Adults with Diabetes

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Abstract

The authors review the science linking depression with diabetes. Some recent heuristic research is identified that highlights progress in the field and is directing future research. Issues in the management of depression in diabetes are outlined, including interactions of depression and insulin resistance.

Introduction

The idea that the mind and body are closely connected is widely accepted. Mental states such as depression are thought to affect physical health or susceptibility to disease and, conversely, being in poor physical health may increase susceptibility to emotional difficulties. Belief in mind-body connectedness is further reflected in our views of treatment, eg, in acceptance of the notion of “mind over matter.” This refers to the capacity of thought and various mental states (strong will, positive attitude, or spiritual harmony) to extricate one from illness and promote health.

Unlike the general public, the US medical community has been widely skeptical of mind-body principles, questioning particularly their evidentiary basis [1]. In this article, the authors discuss the interaction of depression and diabetes, identifying historical influences, recent accomplishments, and the direction of future research. The review is divided into three principle sections. The first summarizes the history of research linking depression with diabetes. The second reviews the literature depicting the impact of depression on diabetes, emphasizing epidemiologic studies identifying depression as a risk factor for developing type 2 diabetes. The third is a discussion of research pertaining to the recognition and treatment of depression in diabetes. The latter two sections are organized to provide historical perspective, identify significant recent research advances, and synthesize the available literature to suggest future research directions. A concluding summary is given in a fourth and final section.

Depression in Adults with Diabetes: Background

Increased prevalence of depression in persons with diabetes has been remarked upon for more than 200 years. Surprisingly, the first mention of the association was one expressing the belief that depression caused diabetes. Writing in 1684, Willis [2] claimed that diabetes was the result “of sadness, or long sorrow.” Willis's causal hypothesis had little if any heuristic impact, and for the next few centuries, when considered at all, depression was

conceptualized as a secondary reaction imposed by the hardships associated with diabetes and not a matter of independent importance.

In the years since Willis, the scientific community showed relatively little interest in investigating the connection between diabetes and depression. Studies that appeared, whether controlled or uncontrolled, were mostly epidemiologic observations reporting an increased prevalence of affective illness in patients with diabetes or, conversely, the increased prevalence of diabetes in patients with bipolar disorder. Research attempts to understand the mechanisms responsible for coprevalence or psychiatric treatment trials were rare. In 1988, Winokur et al. [3] were perhaps the first to suggest that insulin sensitivity was dysregulated in non-diabetic patients with depression. Turkington [4] was among the first to report on the use of antidepressant medication in patients with diabetes. His study showed that antidepressant treatment effectively relieved both pain and depression in patients with symptoms of painful diabetic neuropathy. Despite these important contributions, research in this area remained fragmented.

The number of articles dealing with depression and diabetes written over the past 15 years exceeds the number written during all the years prior to that point. A number of factors have contributed to the upsurge in interest, the first being the development of a reliable and valid approach to psychiatric diagnosis that was suited to doing research. In 1972, researchers in the department of psychiatry at Washington University in St. Louis, Missouri, proposed a method of diagnosing depression and other psychiatric disorders using specific symptoms and severity criteria for each illness [5]. The diagnostic criteria for depression subsequently were adopted for use by the American Psychiatric Association and published in the Diagnostic and Statistical Manual of Mental Disorders. These methods were employed in the Epidemiologic Catchment Area (ECA) program studies that were conducted in the early 1980s and established the prevalence of depression and other mental disorders in the US population.

A 13-year follow-up study of the ECA subjects by Eaton et al. [6] was the first to report the likelihood of developing diabetes was increased in persons diagnosed with depression compared with those who were free of depression. Although other investigators had noted that the onset of depression typically preceded the onset of diabetes (type 2) [7,8], such reports did little to stimulate further research or sway those holding to the presumption that depression was simply secondary to diabetes. The fact that the study by Eaton et al. [6] was population-based and methodologically rigorous with state-of-the-art sampling techniques, modern psychiatric diagnostic techniques, and a statistical approach that controlled for the effects of conventional diabetes risk measures, occasioned a re-examination by scientists and by public health entities such as the National Institutes of Health. This work marked the beginning of numerous population-based studies in the United States and elsewhere showing that depression increases the risk of developing type 2 diabetes [9] and of disease progression in either type 1 or type 2 diabetes [10,11].

Meta-analysis is a statistical approach that allows findings over multiple studies to be combined and analyzed in the aggregate [12–14]. This technique is useful when the number of studies relevant to a hypothesis is small or when the available data are inconsistent. Meta-analysis discourages the practice of selective referencing (ie, citing only those studies that support a hypothesis while omitting those that do not). In the early 2000s, meta-analyses were published that answered three long-standing questions. Does depression occur more often in those with diabetes? Does depression have a negative effect on glycemic control? Does depression increase the likelihood of developing diabetes complications?

Addressing the first question, Anderson et al. [15] analyzed findings across 42 studies. They determined that the odds of depression were doubled in persons with compared to those without diabetes (odds ratio [OR] = 2.0; 95% CI, 1.8 to 2.2) and did not differ by sex or type of diabetes. Although the odds of depression were stable (per the narrow CI), the prevalence of depression was influenced by a number of factors. Depression was significantly higher in diabetic women than in diabetic men (28% vs 18%), in clinical compared with community samples (32% vs 20%), and when assessed via self-report questionnaires compared with psychiatric diagnostic interviews (31% vs 11%). To answer the second question, Lustman et al. [16] analyzed data aggregated across 24 studies. They found that depression was significantly associated with hyperglycemia, the effect size being in the small-to-moderate range (0.17), similar in type 1 compared with type 2 diabetes (0.19 vs 0.16), and larger when depression was ascertained from psychiatric diagnostic criteria than from self-report questionnaires (0.28 vs 0.15). The third question was studied by de Groot et al. [17]. Depression was significantly associated with a variety of diabetes complications including neuropathy, retinopathy, nephropathy, sexual dysfunction, and macrovascular disease, the effect sizes being in the small-to-moderate range (0.17 to 0.32).

Beginning in 1988, treatment trials appeared targeting depression in diabetic patients [18]. They addressed the basic questions of whether depression in diabetes was responsive to antidepressant medication or psychotherapy and whether improvement in depression had any measurable effect on glycemic control. These trials were careful to distinguish the direct glycemic effects of the intervention from those related to improvement in depression symptoms. The initial studies focused on the efficacy of short-term treatment, whereas more recently the efficacy of antidepressant continuation was examined over longer intervals for prophylaxis against depression recurrence. Although to date the number of treatment studies remains small, findings have been encouraging, revealing beneficial effects of both short-term psychotherapy and pharmacotherapy on mood control and of maintenance pharmacotherapy in preventing depression recurrence [8,19]. Nevertheless, depression management remains a vexing problem in clinical practice; acute-phase treatments, although superior to placebo, have modest potency, and recurrence in the face of maintenance treatment is common and often accompanied by glycemic deterioration, especially in younger patients [20]. Recent evidence suggests insulin resistance (IR) may limit the effectiveness of depression treatment, increase the risk recurrence, and require direct management to optimize psychiatric outcomes [21].

Perhaps the largest stimulus for psychosocial research in diabetes in recent years has been the threefold rise in the prevalence of diabetes since 1990 among persons in the United States [22]. For individuals born today, the estimated lifetime risk of diabetes exceeds 35% [23]. Furthermore, despite significant advances in diabetes treatment, fewer than one in three patients is able to maintain glycosylated hemoglobin levels below 7.0%, the level recommended by the American Diabetes Association and required to prevent complications [24]. These facts have prompted a call from patients, care providers, and scientists to expand the search for modifiable risk factors whose treatment could support better glycemic control and diabetes outcomes. As the background materials outlined earlier indicate, the association of depression with diabetes deserves a careful look to determine if depression might be one of these factors.

Impact of Depression in Diabetes

Historical perspective

For many years, the limited interest in depression in diabetes was kindled solely by temporally disconnected epidemiologic observations demonstrating the coprevalence of these conditions. Such efforts had little impact on the broad diabetes community. Research

on depression was slow to develop; that it eventually did may in part reflect the strength of the association. Coprevalence assertions were variously seen as unnecessary restatements of the obvious, as a needless burden to those already unfortunate enough to have diabetes, or somehow a misperception borne of symptom overlap between the two conditions. The meta-analysis by Anderson et al. [15] was important because it demonstrated that approximately one in every four persons with diabetes (type 1 or type 2) had depression severe enough to warrant treatment, settled any remaining controversy over the prevalence of depression in diabetes, and allowed research in this area to expand its focus. Subsequent research demonstrated the important impact of depression in diabetes independently from its prevalence.

Recent research advances

Depression as a risk factor for diabetes—Whether depression can cause incident diabetes has recently been studied, but the data are restricted to longitudinal observation and not experimental models. A landmark study in psychiatric epidemiology by Eaton et al. [6] was the first to examine whether depression was a significant predictor of diabetes. Depression was assessed using a diagnostic interview, and diabetes was assessed by self-report. In this 13-year follow-up of participants ($n = 1715$) from the ECA who were enrolled in 1981, the data suggested that major depression could double the subsequent risk for developing type 2 diabetes. Although the OR was 2.23, the finding did not reach statistical significance (CI, 0.90 to 5.55). The authors noted that a major limitation of their work was the possibility of undetected diabetes resulting from the self-report methods utilized. Only 76 persons met criteria for major depression in 1981 and had complete diabetes data at follow-up, and the number of these individuals who developed diabetes was small ($n = 6$ [7.9%]). Thus, lack of statistical power may have impaired the ability to detect a significant effect. However, the study was important because it questioned whether depression could predict subsequent chronic illnesses such as diabetes—a new concept. In addition, it forced researchers to examine the relationship of depression and diabetes carefully in order to establish the temporal order of these variables.

Kawakami et al. [25] subsequently examined whether depression could increase the risk of developing diabetes in 2380 male employees of a Japanese company. The Zung depression scale was used to examine severity of current depression symptoms. Diabetes was confirmed with a fasting glucose measurement. Over a period of 8 years of follow-up, 41 men developed diabetes. Those individuals with moderate or severe depression at baseline were more than twice as likely to have type 2 diabetes at follow-up compared to those with normal levels of depression at baseline after controlling for covariates (hazard ratio [HR], 2.31; CI, 1.03 to 5.20).

Recently, four large prospective cohort studies have reported that depression is associated with increased risk of diabetes. However, this association is significantly affected by the number and types of risk factor adjustments. Two of these cohort studies included only women who were followed up over a relatively brief interval. In the Study of Women's Health Across the Nation, 2662 women without a history of diabetes were followed up for 3 years [26]. Mean age at follow-up was 46 years. The Center for Epidemiologic Studies depression rating scale (CES-D) was used to assess depression symptoms, and fasting glucose and diabetes self-report were used to assess diabetes. Depression significantly predicted diabetes after adjustments for age, race, site, education, and medication use (OR 1.66; CI, 1.05 to 2.61). After further adjustment for physical activity and waist circumference, this relationship lost significance (OR 1.49; CI, 0.90 to 2.36). In the Nurses' Health Study, an adult female cohort ($n = 72,178$) was examined after 4 years of follow-up to determine the risk of developing diabetes in relation to depression symptoms [27]. Mean

age at follow-up was 58 years. The Mental Health Index of the Medical Outcomes Study Short Form (SF-36) [28] was used to measure depression, and diabetes was assessed by plasma glucose or treatment with hypoglycemic medications. Results indicated that depression symptoms were significantly associated with risk for developing diabetes after adjustment for age (relative risk [RR] 1.55; CI, 1.27 to 1.90). After adjustment for other risk factors, the relationship was modest (RR 1.22; CI, 1.00 to 1.50).

Two recent cohort studies with longer periods of follow-up were inclusive of both genders. An adult group from the ARIC (Atherosclerosis Risk in Communities) cohort ($n = 11,615$) who initially did not have diabetes were followed up for 6 years for the development of type 2 diabetes [29]. Depression symptoms were assessed using the Vital Exhaustion Scale, and diabetes was assessed by serum, glucose, and self-report. The mean age at follow-up was 57 years. Depression symptoms significantly predicted type 2 diabetes after adjusting for age, sex, and education for those individuals in the highest quartile of depression symptoms (relative hazard [RH] 1.63; CI, 1.31 to 2.02). After further adjustment for metabolic and lifestyle factors, the association was less strong but still significant (RH 1.31; CI, 1.04 to 1.64). Participants in the NHANES (National Health and Nutrition Examination Epidemiologic Study) who were free of diabetes at baseline ($n = 6190$) were followed up from 1971 to 1992 [30]. The mean duration of follow-up was 15.6 years and the mean age at baseline was 48 years. Depression symptoms were measured using the depression subscale of the General Well-Being Survey, and diabetes was assessed by death certificates, health care facility records, and self-report. When individuals with the highest number of depression symptoms were compared to those with the lowest, they were more than twice as likely to develop diabetes after adjusting for age, race, and gender (RR 2.52; CI, 1.73 to 3.67). However, after further adjusting for health behaviors, the relationship became insignificant (RR 1.86; CI, 1.27 to 2.71).

Because these four recent studies [26,27,29,30] used differing statistical methods in evaluating the association between depression and incident diabetes, statistical transformations were applied in subsequent reports, converting the data to RR estimates [31,32]. In the studies where depression symptoms were categorized into more than two groups (eg, low, intermediate, high), the risk of the highest group compared with the lowest group was used. Combined estimates of RR were obtained using a meta-analysis approach and weighted averages [33]. The combined estimate was 1.73 after adjustment by age and gender (CI, 1.44 to 2.09) and 1.36 after adjustment for age, gender, and other risk factors (CI, 1.16 to 1.60). These findings provide further evidence that depression is associated with the onset of diabetes. Factors limiting the strength of this conclusion include use of self-report for depression and overrepresentation of women who are at greater risk for depression.

Knol et al. [9] also examined depression as a risk factor for the onset of type 2 diabetes using meta-analysis methods. These investigators included all published studies through January 2005 (irrespective of design) that longitudinally examined the relationship between depression and the onset of diabetes. The previously discussed studies [6,25–27,29,30] as well as three additional studies were included. One of the additional studies was a retrospective cohort analysis using a computerized database of family practices in the Netherlands. Persons were segregated into those who had depression between 1975 and 1979 ($n = 1334$) and age-matched persons who did not have depression ($n = 66,670$) [34]. An increased risk for developing diabetes was determined in the male subset between the ages of 20 and 50 (HR 1.78; CI, 1.21 to 2.62). The database did not distinguish between type 1 or 2 diabetes, yet the authors noted that 97.9% of the subjects were aged 30 years and older when diagnosed with diabetes.

Another study included a cohort of men and women aged 50 years and older from the Rancho Bernardo study ($n = 971$) who were evaluated at two clinic visits (the first from 1984–1987 and the second from 1992–1996) [35]. Mean age at the two visits was 66 and 75 years. Depressed mood (Beck Depression Inventory [BDI] ≥ 11) was a risk factor for type 2 diabetes independent of age, sex, exercise, and body mass index (BMI) (OR 2.5; CI, 1.29 to 4.87). The third additional study was a prospective occupational cohort investigation of men and women ($n = 10,308$) from the Whitehall II study (London-based civil service departments). Social and other risk factors for incidence of type 2 diabetes were examined after an average of 10.5 years of follow-up [36]. Depression was assessed using a depression subscale of the General Health Questionnaire, and diabetes was determined using the World Health Organization definition. Depression was not associated with incident diabetes in men or women, but when new onset of impaired glucose tolerance was included in the analyses, the association was present for men (OR 1.25; CI, 1.0 to 1.6).

When the nine studies were pooled by Knol et al. [9] to estimate RR, a 37% increased risk for developing type 2 diabetes was calculated for depressed adults (RR = 1.37; 95% CI, 1.14 to 1.63) (Fig. 1). Therefore, the cumulative evidence suggests that having depression increases the risk for developing type 2 diabetes. The authors acknowledged the possibility of publication bias but queried prior investigators about unpublished or rejected studies.

Depression as a contributor to increased morbidity and mortality in diabetes

—Recent research has demonstrated that depression likely increases morbidity from diabetes. Using meta-analysis methods, Lustman et al. [16] examined 24 studies that measured the association between depression and glycemic control. Depression was significantly associated with hyperglycemia ($z = 5.4$, $P < 0.0001$) in persons with diabetes (type 1 or type 2), and the association was stronger when standardized interviews and diagnostic criteria rather than self-report measures were used to assess depression. One proposed mechanism for this relationship is that cortisol abnormalities associated with depression have hyperglycemic effects [37]. Depression also causes poor adherence to diet, physical activity, and medication regimens, factors that could further contribute to poor glycemic control. Depressed patients with diabetes have hemoglobin A_{1c} (HbA_{1c}) levels that average 0.5% to 1.0% higher than those seen in nondepressed patients. Given that a 1% increase in HbA_{1c} is associated with an 18% increase in risk of coronary heart disease, the degree of glucose dysregulation associated with unrecognized or untreated depression is significant [38].

Depression is also linked to higher complication rates in persons with type 2 diabetes. de Groot et al. [17] used meta-analysis methods to assess the association between depression and diabetes complications across 27 studies. The association was significant ($z = 5.94$, $P < 0.00001$), with depression being associated with retinopathy, nephropathy, neuropathy, macrovascular complications, and sexual dysfunction. It was suggested that prospective longitudinal studies be performed to determine the directionality of the relationships and the pathways that mediate them.

Whether depression actually increases cardiac morbidity and mortality in persons with diabetes has been a recent focus of research. Clouse et al. [10] hypothesized that depression played a role in increased cardiac morbidity for women with diabetes. They examined the outcome in relation to depression status at baseline of women ($n = 76$) being treated for diabetes (type 1 or type 2) who were part of a diabetes registry. Survival analysis was used to compare the rate of incident coronary heart disease events over a 10-year period in the subset with major depression ($n = 16$) to those without major depression ($n = 60$) at the initial registry visit. The development of coronary heart disease events was more rapid in those women who were depressed ($P < 0.01$). Depression was also an independent predictor

of coronary heart disease events in an age-adjusted multivariate model that controlled for other conventional cardiac risk factors.

More recently, Egede et al. [39••] examined participants of the NHANES study ($n = 10025$) to evaluate the effect of depression on mortality (all-cause and coronary heart disease) in individuals with and without diabetes. In 1982, adults were evaluated for depression (using the CES-D), demographic characteristics, lifestyles, and comorbidities. Follow-up data on cause of death were ascertained through the National Death Index. For those persons who had both depression and diabetes, all-cause mortality was greatest (HR 2.50; CI, 2.04 to 3.08) compared with those having depression alone (HR 1.20; CI, 1.03 to 1.40) or diabetes alone (HR 1.88; CI, 1.55 to 2.27). Coronary heart disease mortality was also greater in those with both diagnoses (HR 2.43; CI, 1.66 to 3.56).

Zhang et al. [40] conducted a survival analysis of the NHANES I data. They found that significant depression symptoms (CES-D > 16) predicted increased mortality in persons with diabetes but not in persons without diabetes. After controlling for sociodemographic, lifestyle, and health status variables, persons with diabetes and significant depression symptoms had a 54% greater mortality than those with fewer symptoms ($P = 0.004$). Katon et al. [41] followed over 4000 HMO patients with type 2 diabetes (who were part of the Pathways study) to determine whether level of depression (none, minor, major) affected mortality rate over a 3-year period. The Patient Health Questionnaire-9 was used to assess depression. There were fewer deaths in patients who did not have depression (8.3%) when compared to those with minor and major depression (13.6% and 11.9%, respectively). Using a proportional hazards model that adjusted for age, sex, race/ethnicity, and education, those with minor depression had 1.67 times the mortality of those without depression ($P = 0.003$), and those with major depression had 2.3 times the mortality ($P < 0.0001$).

Synthesis and future directions

The evidence is mounting for an association between depression and incident diabetes and for an association of depression with increased morbidity and mortality from diabetes. Existing studies have used different methods of assessing depression, different methods of determining diabetes, and different intervals for the collection of these measurements. Comprehensive depression history, including a family history, age of onset of depression, number and duration of depressive episodes, as well as number and type of depression treatment should be considered to better elucidate the relationship between depression and diabetes. Studies should also examine the effect of depression on incident metabolic syndrome, because diabetes typically remains undiagnosed for at least 5 years after onset of glucose intolerance. Prospective observation will be needed to better determine cause of death.

Recent emphasis by the National Institutes of Health for understanding the molecular links between obesity, IR, and type 2 diabetes [42] should also include an understanding of the severity and duration of depression and its impact on the progression of diabetes. This will be particularly important if treatment of depression and other mood disorders in young, obese individuals can prevent the onset of metabolic syndrome and type 2 diabetes. For those individuals who develop diabetes, a record of the specific complications and when they began will be important, as complications could precipitate or augment depression in persons with diabetes. Lifestyle factors (eg, obesity, smoking, sedentary activity) will also need consideration, as they contribute significantly to the onset and course of depression as well as diabetes. Finally, identification of the susceptibility of genes for diabetes [42], as well as depression and other mood disorders, may allow for the development of drugs that could assist in the management of both disorders making treatment less burdensome to the patient.

Recognition and Treatment of Depression in Diabetes

Historical perspective

Research on the treatment of depression in diabetes helped establish the legitimacy of psychosocial research in diabetes. Turkington [4] reported on the first randomized controlled study showing the use of antidepressant pharmacotherapy in patients with painful diabetic neuropathy. In this study, short-term treatment (8 weeks) with imipramine hydrochloride, a tricyclic antidepressant, resulted in complete remission of lower extremity pain with concomitant relief of depression symptoms. Using this study as a template, Lustman et al. [18] conducted a randomized, double-blind, placebo-controlled trial of nortriptyline in diabetic patients with or without depression. Plasma nortriptyline levels were used to guide treatment and therapeutic doses were given to both depressed and nondepressed subjects. The researchers were able to detect both antidepressant and hyperglycemic effects of nortriptyline. Path analysis revealed that, independently of treatment, improvement in depression was associated with significant improvement in glycemic control. Each one-point reduction in the BDI was associated with a 0.04% reduction in HbA_{1c}. The finding that improved mental function promoted improved physical function provided additional impetus for further controlled clinical trials. These subsequent trials reaffirmed the efficacy of short-term depression treatment (fluoxetine [43] and cognitive behavioral therapy [44]) in the face of diabetes, and replicated the antihyperglycemic effect of depression improvement [44].

Recent advances

Diabetes care has historically focused on improving and maintaining glucose control measured and monitored as HbA_{1c}. The efficacy of this approach has been demonstrated in large randomized clinical trials, with reductions in HbA_{1c} leading to significant sustained reductions in microvascular and neuropathic complication rates. The evidence with regard to macrovascular complications is less compelling, an important fact because atherosclerosis accounts for most of the morbidity and mortality in diabetes. Other factors present long in advance of overt type 2 diabetes, including obesity and IR, contribute to macrovascular disease. Current approaches to diabetes management include use of treatments that target these factors more directly. Recent clinical evidence suggests that depression treatment may also have beneficial effects on these management targets.

Insulin sensitivity improves during depression treatment—Recently, Okamura et al. [45] compared 20 nondiabetic patients with depression to an age-, sex-, and BMI-matched nondepressed control group using oral glucose tolerance tests (OGTTs) and frequently sampled intravenous glucose tolerance tests (FSIGTTs). The minimal model analysis from the glucose tolerance test data was used to assess IR. SI, the index of insulin sensitivity determined from FSIGTT, was significantly lower in depressed compared with nondepressed subjects (6.0 ± 2.5 vs 13.8 ± 8.6 , $P = 0.0005$). This confirmed the association of depression with increased IR in nondiabetic individuals. Depressed subjects were also compared before and after depression treatment. Each patient was given tricyclic antidepressants and maintained on a diet of 1800 to 2200 kcal/d with no exercise therapy. A significant increase in SI was observed following treatment (10.7 ± 7.5 , $P < 0.01$) with no concomitant changes in BMI, fasting blood glucose, or other indices of glucose effectiveness. Changes in OGTT and FSIGTT during treatment were similarly significant; the OGTT results are displayed in Figure 2.

Improvement in IR during depression treatment was also reported in a treatment trial by Lustman et al. [21] of 93 patients with type 2 diabetes and major depressive disorder (MDD). Patients received 10 weeks of open-label acute-phase treatment with bupropion. Those who completed the acute phase ($n = 75$) and remitted ($n = 63$) continued bupropion at

the remission dose and were followed in the maintenance phase (24 weeks) until attrition ($n = 8$) or relapse of MDD ($n = 0$). BMI, total fat mass, and HbA_{1c} decreased, and composite diabetes self-care improved over the acute phase ($P < 0.01$ for each), effects that persisted through the maintenance phase for BMI, HbA_{1c}, and self-care. Reductions in BMI and depression severity independently predicted lower HbA_{1c} following acute-phase treatment, whereas only reduction in depression severity predicted HbA_{1c} over the maintenance interval.

Maintenance antidepressant pharmacotherapy is more effective than placebo in preventing recurrence of MDD in diabetes—

Although depression treatment leads to improvements in mood and glycemic control, these benefits, particularly those accompanying depression remission with antidepressant medication, are short-lived [18,43,46,47]. As few as 40% of depressed diabetic patients remain well in the year following successful depression treatment [47], one in seven patients suffer chronic depression unresponsive to available treatments [8], and recurrence of depression is generally accompanied by a deterioration in glycemic control [46,47]. As few as 10% of patients are able to remain depression free over 5 years of observation and experience an average of one episode annually.

Maintenance antidepressant treatment, the practice of continuing patients on medication beyond the point of recovery from MDD, is effective for preventing recurrence in persons without diabetes. The efficacy of this maintenance approach with sertraline was recently studied in a multisite, double-blind, placebo-controlled trial of patients with diabetes [19]. Sertraline conferred significantly greater prophylaxis against depression recurrence than did placebo (HR 0.51; 95% CI, 0.31 to 0.85; $P = 0.02$). Elapsed time before one third of patients recurred was increased from 57 days in placebo to 226 days in sertraline-treated patients. HbA_{1c} levels decreased during the open treatment phase ($-0.4\% \pm 1.4\%$, $P = 0.002$) and remained significantly lower than baseline during depression-free maintenance ($P = 0.002$).

Synthesis and future directions

Data available from acute- and maintenance-phase depression treatment trials in diabetic patients attest to the efficacy and utility of depression treatment as well as its beneficial effects on glycemic control. However, the potency of treatment is rather modest overall. In the acute phase, antidepressant pharmacotherapy increases the likelihood of recovery from the index episode by 20% to 30% compared with placebo. Results were significantly more impressive with cognitive behavior therapy, with treated patients being 57% more likely to remit. The potency of maintenance approaches is similarly underwhelming, with approximately one in two patients initiated on therapy recovering from the index episode [19,48••] and as few as one in four remaining depression free over the subsequent year [19].

The recent studies by Okamura et al. [45] and Lustman et al. [21] further emphasize the complexity of the relationship between IR and depression. Insulin sensitivity improved during depression treatment and remained improved throughout the subsequent depression-free interval. Significant improvement in BMI and total body fat (both surrogate markers of IR) occurred with bupropion treatment and portended a favorable depression outcome. Fully 87% of bupropion-treated patients achieved depression remission and none of these patients recurred during the subsequent 6 months of observation. Further studies are needed to see whether antidepressant regimens that include direct treatment of IR may improve depression outcomes in persons with diabetes.

Conclusions

Recent research advances have provided new and exciting information regarding the importance of depression in diabetic patients. Emerging appreciation of the IR linked to depression creates a pathophysiologic platform for positioning depression as a risk factor for the development of type 2 diabetes, a contributor to and accelerator of diabetes complications, and a modulator of glycemic control. Findings from acute- and maintenance-phase depression treatment in diabetic patients and acute-phase depression treatment in nondiabetic patients strongly suggest that modifying depression status can improve insulin sensitivity and produce sustained reduction in HbA_{1c}. Further investigation is required to confirm these observations and secure the mechanisms behind the observed changes.

Because the identification of modifiable risk factors in diabetes is of paramount importance, research into the relationship of depression and diabetes should accelerate. In particular, treatment strategies that produce the greatest likelihood of sustained depression-free intervals must be developed, strategies that likely will vary by subgroups within the diabetes community (eg, by age, course of depression, degree of complications). Antidepressant agents should be examined for their specific effects on insulin sensitivity, not only depression symptoms. Treatment approaches for the depressed diabetic patient that maximally improve both depression and glycemic control should be created, with the focus shifting away from separate management of the two conditions in isolation.

The story linking depression and diabetes is a hallmark example of the methods by which careful observational research can lead to pathophysiologic explanation and, ultimately, better management for the patient with disease. Willis' observations three centuries ago—that diabetes followed long sorrow—are now substantiated by carefully performed epidemiologic investigations, and physicians can no longer disregard depression solely as an inconsequential byproduct of disease hardships. Some available information now quantifies the potential benefit of depression symptom reduction in terms of improved glycemic control and reduced likelihood of complication occurrence. Whether these benefits can actually be attained in clinical practice by sustained attempts at depression management in the diabetic patient is an important effectiveness issue that must be addressed.

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based HMO. Patients receiving the intervention ($n = 164$) were significantly less depressed at the 6- and 12-month follow-up points than those who received usual care treatment ($n = 165$). Glycemic control improved during treatment but did not differ between treatments.]

Figure 1.

Forest plot displaying the relative risk (RR) 95% CI of each study and the pooled RR and 95% CI using both fixed and random effects models. (*From Knol et al. [9]; with permission.*)

Figure 2.

Plasma glucose (A) and insulin (B) levels during oral glucose tolerance testing in depressed patients before (solid line) and after (dotted line) treatment with imipramine. Data are reported as the mean plus or minus standard deviation. Asterisk indicates P is less than 0.05. (From Okamura et al. [45]; with permission.)