Clinical Focus

Depressed Diabetics: A Neuroimmunologic Syndrome?
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Needs Assessment: There is ample evidence to support the comorbidity of diabetes and depression. While the exact mechanism is unknown and is likely multifaceted, it is worthwhile to examine the neuroimmunologic mechanisms that contribute to both types of diabetes, discuss the role of neuroinflammatory markers and depression, and understand the role of γ-aminobutyric acid as a possible marker for depression and its relationship to the anti-glutamic acid decarboxylase antibody.

Learning Objectives:
• Recognize the high rates of comorbidity between depression and diabetes.
• Define the pathophysiologic distinction of type-1 and type-2 diabetes mellitus and their relationship to depression.
• Recognize the role of the anti-glutamic acid decarboxylase antibody and its potential role in γ-aminobutyric acid synthesis.
• Comprehend the role of proinflammatory cytokines in “sickness behavior.”

Target Audience: Primary care physicians and psychiatrists.

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Abstract
Multiple studies have shown that depression is more common in patients with type-1 and type-2 diabetes than in healthy controls. Substantial evidence indicates that cytokines, such as the interleukins, interferons, tumor necrosis factor, and other immune system signaling molecules, influence mood in humans. Both type-1 and type-2 diabetes are accompanied by altered levels of circulating cytokines, which may increase susceptibility to depression. Recent evidence also suggests that the chief brain inhibitory neurotransmitter, γ-aminobutyric acid (GABA), plays a critical role in depression. Antibodies to glutamic acid decarboxylase, the chief synthetic enzyme for GABA in the brain, are present in the serum of many patients with type-1 diabetes, may influence GABA function, and provide a second immunological mechanism by which diabetes might induce depression.

Introduction
In recent years, a substantial amount of literature has accumulated demonstrating the clinical association between diabetes mellitus (DM) and major depressive disorder (MDD). While a significant effort has been made to catalogue the serious medical, social, and financial complications associated with the comorbidity of these disorders, little progress has been made in identifying how the mechanisms of pathogenesis may be related physiologically. Although there are several potential areas of intersection, this article is focused mainly on examining the more recent evidence involving the interaction between the central nervous system (CNS) and the immune system, a relatively new field known as psycho-

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neuroimmunology. After reviewing the evidence that MDD and diabetes are associated, it discusses two immunological mechanisms by which diabetes might influence mood.

**Epidemiology and Pathophysiology of Diabetes Mellitus**

DM is a disorder of carbohydrate metabolism caused by a relative or absolute deficiency of insulin resulting in hyperglycemia. If poorly controlled, patients are likely to develop end-organ complications, including nephropathy, neuropathy, retinopathy, and atherosclerosis. It is estimated that approximately 5.1% of the United States population suffers from DM. Although the net effect of insulin deficiency results in similar complications, DM is further classified into two pathophysiologically distinct illnesses: type 1 (T1DM) and type 2 (T2DM).

T1DM (also known as insulin-dependent diabetes mellitus) has a prevalence of <1% with onset usually before 30 years of age. It is an autoimmune disease associated with the presence of several autoantibodies and an inflammatory response in the pancreas called insulinitis. Diabetes symptoms appear acutely, by which time approximately 80% of the insulin-producing β-cells have been destroyed by the process. Several pancreatic molecules are targeted by autoantibodies, including insulin, glutamic acid decarboxylase (GAD), and islet cell antibody-52.

T2DM is the most prevalent form of diabetes, with onset usually after 40 years of age. It is generally associated with a dysmetabolic syndrome which includes the following features: central obesity (increased waist-hip ratio), abdominal girth >40 inches in males and 35 inches in females, hyperlipidemia (characterized by high triglycerides, low high-density lipoproteins, and high low-density lipoproteins), and borderline hypertension.

The pathophysiology of T2DM may involve an inflammatory process with a far more insidious onset than in T1DM. The plasma glucose elevates over a period of years rather than weeks as in T1DM. Autoantibodies are less frequently associated with T2DM, and there is a relative insulin deficiency due to inadequate insulin secretion and resistance to insulin action in target tissues.

**Diabetes Mellitus is Frequently Associated with Major Depressive Disorder**

It is well established that diabetes is associated with increased prevalence rates of MDD compared to those seen in the general public. Lustman and colleagues described depression and/or depressive behavior as more common among diabetics compared to controls in 9 out of 10 studies. In a review of 20 studies, Gavrard and colleagues concluded that both the 14.7% prevalence rate and the mean level of depressive symptoms in diabetic subjects are significantly increased compared to control samples. In a more recent meta-analysis of 42 studies, MDD was found to be present in 11% of diabetic subjects and elevated depressive symptoms were found in 31% of diabetic subjects. In the 20 studies reviewed that included a comparison sample, the odds ratio of diabetics having MDD was twice that of the nondiabetic controls.

A significant barrier to formulating a more advanced biological interpretation of comorbidity studies is the tendency to group the two types of diabetes into one cohort, which makes it difficult to compare the rates of MDD in the specific subtypes. In the largest controlled study to specifically address the comorbidity between depression and T1DM, Popkin and colleagues assessed a cohort of 75 patients with long-standing T1DM. Using the Diagnostic Interview Schedule, lifetime prevalence of MDD was found to be markedly elevated at 22.9% for type-1 diabetic females and 25.9% for type-1 diabetic males. This was significantly higher than the MDD prevalence rates in the 34 first-degree relatives and the general population assessed in this study.

Kawakami and colleagues performed a controlled study regarding the relation of depression and T2DM. After controlling for known risk factors, it was found that Japanese men with significant depressive symptoms had a 2.3 relative risk of developing T2DM compared to nondepressed controls over an 8-year period. In comparing depression prevalence rates between adult T1DM and T2DM in all available controlled studies that specified the subtype of diabetes, Anderson and colleagues found the prevalence of MDD to be 21.7% for type 1 and 16.5% for type 2, demonstrating that both types of DM are associated with higher rates of MDD than those of control subjects (6.4% and 8.6%, respectively).

**Common Pathophysiology**

It is becoming increasingly clear that depression is a multisystem disorder with endocrine, vascular, neural, immunologic, and psychosocial components. Clearly, a patient with diabetes experiences morbidity and stresses that may contribute to depression; depression, in turn, can lead to poor compliance and self-care in diabetics. However, increasing evidence suggests that the two disorders may be closely related beyond these psychological connections, on a physiological level. The relationship between MDD and DM is likely to be complex, and it would be difficult to establish a clear directional causative relationship. Additional factors may be involved in the pathogenesis of both disorders. It is likely that both subtypes of DM share several of these factors, but there may also be unique factors associated with the separate subtypes. It is beyond the scope of this article to examine all the potential mechanisms of interaction between DM and MDD; consequently, it will focus solely on two potential mechanisms through which disease-related immunologic factors may contribute to the high rates of comorbidity between DM and MDD (Figure).

**Potential Role of Pro-inflammatory Cytokines**

Perhaps one of the most interesting areas to explore is the role of pro-inflammatory cytokines in depression and diabetes. Cytokines are small intracellular signaling proteins produced by lymphocytes, leukocytes, and other cells that are necessary in mediating host defense and regulating immune responses, the acute phase reaction, and hematopoiesis. It is now well accepted that there is abundant cross-talk between the immune system and the CNS, even though the CNS has traditionally been thought of as an immunoprivileged compartment. This bidirectional communication is thought to be mediated partly by cytokines. Acute peripheral or central administration of pro-inflammatory cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α),...
induces anhedonia, reduced locomotor and sexual activity, and decreased social interaction in rodents. These symptoms are collectively known as “sickness behavior,” but in humans are also characteristics of MDD.

Similarly, treatment of cancer with certain cytokines induces depression that can be reversed by administration of antidepressants, and has been associated with a reduced availability of the serotonin relevant amino acid precursor, tryptophan. Circulating IL-6 and TNF-α stimulate corticotropin-releasing hormone, thus activating the hypothalamic pituitary axis causing hypercortisolemia, which may be involved in the etiology of depression.

In addition to potential direct effects on neurons, the microenvironment in the CNS may be altered by the induction of glial secretion of factors that affect neuronal function. TNF-α, in particular, has been implicated in maintenance of synaptic strength by controlling the surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors.

Finally, it has recently been shown that pro-inflammatory cytokines can inhibit the process of adult neurogenesis, also potentially involved in the etiology of depression. It is therefore reasonable to hypothesize that cytokines produced at sites of inflammation contribute to the induction and/or propagation of depressive-like behavior. Conversely, depression in humans leads to a lower response of immune cells to immune challenges, such as vaccination or infection, by interfering with the cytokine network.

Some studies in the literature have linked increased plasma levels of pro-inflammatory cytokines with MDD. For example, Mikova and colleagues found that serum TNF-α was significantly increased in depressed patients. A similar result was obtained in a study examining the association between depressed mood in older adults and plasma levels of IL-6, TNF-α, and C-reactive protein, an acute-phase reactant. Individuals with high plasma levels of two out of these three molecules had a significantly higher rate of depressed mood compared to subjects with low levels. Interestingly, these elevated cytokine levels may be normalized by administration of certain antidepressants. In one particularly interesting study, TNF-α levels were normalized by amitriptyline, but only in those patients whose depression responded to the treatment. In several studies, some elevated cytokine levels could be normalized with certain antidepressants, but other investigators have found little or no effect using a wide range of drugs.

Unfortunately, the design of these population studies does not allow for conclusions pertaining to the sequence of events, but it is certainly tempting to combine the data from the human and animal studies and speculate that the increased levels of pro-inflammatory cytokines or other immune mediators are involved in the etiology of depression. This hypothesis also provides a possible explanation for the link between MDD and several major medical diseases, including diabetes. Specifically, overproduction of TNF-α and other cytokines is seen in patients with T1DM and other autoimmune diseases as a direct result of the inflammatory process.

In T2DM, excesses of IL-6, TNF-α, and other inflammatory markers have been shown to be present.

In summary, there is a fair amount of circumstantial evidence connecting MDD with increases in serum levels of pro-inflammatory cytokines, such as those frequently produced by medical disease states. The existing animal studies are promising but difficult to relate to human MDD because they involve very high doses of acutely injected cytokines. Thus, more sophisticated experimental design is needed to ascertain whether these mediators are directly involved in the etiology of depression.

### Potential Role of Autoantibodies

A second mechanism through which diabetes-related effects on the immune system might mediate the emotional, cognitive, and behavioral symptoms of MDD is through direct effects of autoantibodies on the functioning of the γ-aminobutyric acid (GABA) neurotransmitter system. GABA is the primary inhibitory neurotransmitter in the brain. Dysregulation of GABAergic activity is increasingly implicated in the neurobiology of mood disorders. Supporting evidence comes in three forms: first, animal studies show that stress can change GABAergic function and that GABA-modulating agents can alter behavior in animal models of depression. Second, antidepressant and mood-stabilizing medications have been shown to have GABAergic effects. Third and most convincingly, GABAergic abnormalities and reduced GABA concentrations have been demonstrated in depressed patients.

As mentioned above, there are autoantibodies directed toward the pancreatic islet cells in T1DM. One of the most abundant autoantibodies, pres-
ent in approximately 80% of recently diagnosed T1DM adolescents, targets GAD (GAD-Ab). GAD is the principal synthetic enzyme catalyzing the conversion of glutamic acid to GABA and carbon dioxide. It is present in at least two molecularly distinct forms, termed GAD65 and GAD67. Could circulating GAD-Ab impair the function of the GABAergic system in the brain and contribute to the increased rates of MDD in associated with T1DM?

In humans, stiff person syndrome (SPS) may serve as an example of an autoimmune mediated deficit in GAD activity, illustrating the relationship between disrupted GABAergic function and neuropyschiatric disorders. SPS is a rare disorder characterized by progressive muscle stiffness, chronic rigidity, and spasms. The disorder is frequently associated with high GAD65 antibody titers. The presence of GAD-Ab has been demonstrated in the cerebrospinal fluid (CSF) of patients with SPS. Several psychiatric disorders have been reported in individuals with SPS, including disorders believed to be related to GABAergic dysfunction, such as anxiety, alcoholism, and depression.

The anti-GAD antibody found in T1DM initially appears at a time surrounding the diagnosis of T1DM and slowly decreases over several years. This timing is interesting since two studies have found the incidence of depressive symptoms and anxiety to peak in the first 2 years after the diagnosis of T1DM in adolescents. These GAD-Ab found in T1DM are similar to those found in SPS but are usually at lower concentrations and appear to have distinct dominant epitopes. Although antibodies to both isoforms of the GAD enzyme have been detected, GAD65 is the predominant antigen. The presence of GAD-Ab has been correlated with existence of specific clinical features of diabetes.

As stated above, there are multiple reports demonstrating reduced GABA levels in individuals with MDD. This is best characterized by a markedly increased percentage of depressed individuals having decreased GABA content in plasma, CSF, and the brain. Furthermore, recent evidence suggests treatment of depression is associated with a normalization of brain GABA content. Considering the frequent presence of GAD-Ab in T1DM individuals in light of the emerging association between MDD and impaired GABA function, it is intriguing to consider the possible link between the GAD-Ab titers and increased rates of MDD in T1DM. In support of this hypothesis, a recent study found the prevalence of anti-GAD65 positivity to be over four times greater in bipolar patients compared to healthy controls.

Abnormalities in the GABAergic system have been reported in rodent models of T1DM. To date, most of the studies have used the streptozotocin (STZ)-diabetic rat model to study this pathophysiological relationship. STZ exposure has been shown to reduce GABA content in the plasma, retina, superior colliculus, hypothalamus, and brainstem. Direct evidence suggesting that the altered GABAergic function associated with STZ-induced diabetes is related to behavioral changes was recently provided by Gomez and colleagues. They demonstrated a strong negative correlation between the lower extracellular striatal GABA levels found in the STZ rat and immobility time on the forced swim test. These studies lend support to the hypothesis that impaired GABAergic function is associated with STZ model of diabetes in rodents, and is likely to have direct consequences on behaviors frequently used in models of depression and anxiety. However, future studies are required to elucidate the specific relationship of GAD-Ab, altered GABA function, and the depressive symptoms commonly seen in T1DM.

**Conclusion**

Clearly, comorbid MDD impairs the overall ability to function, thus further threatening the health of the diabetic patient. Even when controlling for severity of diabetes, those with comorbid MDD experienced more severe symptoms than nondepressed diabetics and were more likely to be noncompliant with treatment interventions. From a financial aspect, overall cost of care for depressed diabetics was 4.5 times higher than for nondepressed diabetics, even when controlling for severity of diabetes and other medical illnesses. Yet little progress has been made in elucidating the primary mechanisms underlying the increased comorbidity of these two illnesses.

While in the past the psychosocial burdens of diabetes were most commonly considered to be a primary cause for the onset of depressive behaviors, emerging literature suggests a need to explore more direct biological links to further understand the high rates of comorbidity. Neuroimmunology provides an exciting area of exploration that may elucidate shared mechanisms in the pathogenesis and pathophysiology of both disorders. Beyond the relationship between diabetes and depression, advances in the understanding of neuroimmunologically mediated disease processes could help explain the association of T1DM with several other neuropsychiatric disorders. Lastly, and perhaps most importantly, insights into potential immune-mediated mechanisms underlying the relationship between diabetes and MDD could have a significant impact on the broader areas of psychoneuroimmunology and mental illness in general.

**References**


