

## EDITORIAL

# Do individuals with both diabetes and depression have an increased mortality risk?



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“Diabetes and depression comorbidity ... creates a potentially life-threatening situation. It is crucial for patients and clinicians to address the prevention and management of these conditions concurrently.”



Globally, the prevalence of depression and diabetes is markedly high. The rapid increase in the prevalence of these conditions, particularly in developed countries, suggests a trend of epidemic proportions. It is projected that the global prevalence of diabetes will increase from 6.4% (affecting 285 million adults) in 2010 to 7.7% (affecting 439 million adults) by 2030 if no steps are taken to slow or reverse the diabetes epidemic [1]. Depression is generally more common in women than in men, and it is estimated that 6.7% of American adults experience a depressive episode in a 12-month period [2]. The estimated lifetime risk of depression is even greater, at 20% for women and 12% for men [3]. Studies have found that diabetes and depression are highly correlated and a bidirectional association has been suggested [4]. Clinically significant depressive symptoms affect more than one fifth of patients with diabetes, nearly twice as many as those without diabetes [5].

Accumulating evidence has demonstrated that the combination of diabetes and depression could substantially increase an individual's risk of mortality [6–8]. Black

*et al.* observed a higher risk of mortality for individuals with a coexisting diabetes–depression combination [6]. The relative risk (RR) was 4.59 over 7 years of follow-up in a sample of 2830 Mexican–Americans aged 65 years or older, compared with those free of depression and diabetes. In this study, participants with diabetes only or lifetime depression only were also at a higher risk of death with a RR of 1.64 and 1.51, respectively. Egede and colleagues found a 2.5-fold increase in mortality risk for individuals with concurrent diabetes and depression among 10,025 participants aged 25–74 years old in the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (1982–1992), compared with those without either condition [7]. The mortality risk was also significantly higher for diabetes only (RR = 1.88) or lifetime depression only (RR = 1.20). In a large cohort study of more than 78,000 women aged ≥54 years from the Nurses' Health Study we found that women with diabetes had a 35% elevated risk of death, women with depression had a 44% increased risk, and participants with

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both diabetes and depression had double the risk of death, compared with those women without either condition [8]. These prospective studies provide consistent and strong evidence that coexisting diabetes and depression is a dangerous and even fatal combination.

There are multiple and complex causes of increased mortality among patients with diabetes and depression. It is well established that diabetes is strongly linked to cardiovascular disease and mortality [9]. Mounting evidence, however, suggests that depression could also predict the onset of cardiovascular disease [10] and increase the risk of total mortality [11]. Depression is associated with a series of endocrine and hormonal dysfunctions, including insulin resistance [12], inflammation [13], increased hypothalamic–pituitary–adrenal axis activity and sympathetic tone, decreased heart rate variability, cardiac fibrillation threshold and altered thrombogenesis [14]. Alterations in platelet serotonin receptors and increased catecholamine and serotonin levels associated with depression may also promote platelet clumping and subsequent thrombosis [15]. The situation is even worse in diabetic patients in that the coexistence of depression in diabetic patients is associated with poor glycemic control [16], an increased risk of diabetes complications [17], poor adherence to diabetes management [18] and reduced health-related quality of life [19]. Moreover, diabetes and depression are both linked to unhealthy behaviors, such as tobacco use, poor diet quality, obesity, sedentary lifestyle and inadequate exercise, and those unhealthy behaviors have been clearly identified as risk factors for poor physical health and increased mortality.

Diabetes and depression comorbidity critically impacts health outcomes, and creates a potentially life-threatening situation. It is crucial for patients and clinicians to address the prevention and management of these conditions concurrently. Disease management for diabetes only and for depression only can improve the health outcomes for patients with each of these medical conditions. A meta-analysis that synthesized the results from 14 clinical trials suggested that various antidepressant therapies (psychotherapy, pharmacotherapy or combined care) were effective in reducing depressive symptoms in diabetic patients [20]. However, the investigators noted that these treatments had little effect on glycemic control, and concluded that “improvement of the general medical condition, including glycemic control, is likely to require simultaneous attention to both

conditions” [20]. The medical care of patients with multiple chronic diseases, particularly patients with coexisting physical and psychological conditions, accounts for the majority of healthcare costs in the USA [21]. These patients, however, are often treated inadequately at the point of care [10]. A recent single-blind, randomized controlled trial in 14 primary care clinics in an integrated healthcare system in Washington State assessed the effects of collaborative care for patients with depression and chronic illness [22]. A total of 214 participants with poorly controlled diabetes and/or coronary heart disease and coexisting depression were enrolled in the trial and randomly assigned to the usual-care group or to the intervention group. In the intervention group, a medically supervised nurse working with each patient’s primary care physician provided guideline-based, patient-centered management of depression and chronic disease. In comparison to the usual care group, patients in the intervention group had a greater overall 12-month improvement in several biomarkers (glycated hemoglobin, low density lipoprotein-cholesterol and systolic blood pressure), and reduced depressive symptoms. Patients in the intervention group were also more likely to have a better quality of life and greater satisfaction with care received for diabetes and/or coronary heart disease and depression [22]. Based on these findings, an intervention involving the collaborative management of depression and other chronic diseases seems likely to significantly improve the control of both coexisting conditions. Further research is needed to examine the long-term effects of this collaborative care strategy on cardiovascular disease incidence and mortality risk.

Several clinical trials have emphasized the importance and success of lifestyle changes in the prevention of diabetes. In a meta-analysis of published diabetes prevention trials, Gillies *et al.* reported that lifestyle interventions (diet and/or exercise) reduced the incidence of diabetes by half (pooled hazard ratios: 0.51; 95% CI: 0.44–0.60) compared with standard advice [23]. Results from two major diabetes prevention trials with a longer-term follow-up are more encouraging. In the Finnish Diabetes Prevention Study, there was a 43% reduction in the relative risk of developing diabetes between the lifestyle intervention and control group after a median of 7 years [24]. Similar findings were observed in the China Da Qing Diabetes Prevention Study with a 20-year follow-up, with a 51% lower incidence of diabetes during the active intervention period (6 years) and

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a 43% lower incidence during another 14 years of follow-up among those in the combined lifestyle intervention group compared with control participants [25]. The current challenge for diabetes prevention is how to translate the findings from these clinical studies into communities and the larger global population.

Very little is known about how to prevent the onset of depression and whether prevention is even possible. A growing body of epidemiologic evidence has shown that obesity [26], unhealthy diet pattern [27] and physical inactivity [28] may play an important role in the incidence of depression. Whether overall lifestyle, socioeconomic status and physical function act as causal agents or indirectly impact the incidence of depression remains unclear. Data from randomized controlled trials demonstrating the efficacy of weight control, healthy eating and exercise on the prevention and management of psychiatric disorders is limited. This exciting area of research requires further investigation before informed recommendations can be made.

A large number of diabetes cases are undiagnosed [102]. Additionally, physician recognition of major depression is generally considered low, and the prevalence of untreated mental disorders is relatively high in the general population [29], particularly in patients with Type 2 diabetes [30]. In order to further research efforts, accurate diagnosis of diabetes and depression and screening for high-risk individuals are crucial. Results from the Collaborative Psychiatric Epidemiology Surveys (CPES) reported that less than half of Americans with recent major depression have used depression therapies and guideline-concordant therapies in the past year, particularly for Mexican–American and African–American individuals [31]. Patients need to tell their doctors if they are feeling depressed, and doctors also need to be watchful for signs of depression in their diabetic patients. A major obstacle in this process is that it is difficult to distinguish the symptoms of depression from the symptoms of poor management of diabetes and diabetes distress. For example, fatigue, gain or loss of weight, change in appetite and sleep disturbances

are common symptoms of both depression and poor diabetes management. Other obstacles include social stigma and negative perceptions associated with disease diagnosis and mental illness, financial constraints and side effects of antidepressant treatment (particularly weight gain). In addition, mental health specialists are separated from general medical health services in the healthcare system. Primary care physicians may not have adequate knowledge of mental health problems and its consequences for diabetic patients. Therefore, a collaborative and sufficient referral network between primary care physicians, endocrinologists and psychiatrists is needed.

In summary, depression and diabetes comorbidity is common and associated with serious health risks and an elevated risk of mortality. The magnitude of these concurrent health issues is rapidly approaching epidemic proportions. Depression screening in diabetic patients is crucial for the proper treatment of both depression and diabetes. Collaborative medical care in clinical settings aimed at providing adequate psychological management and support should be considered and incorporated into standard diabetes care. Screening for and early detection of depression in diabetic patients are needed and upon diagnosis, treatment of depression should be a priority for diabetic patients. Lifestyle interventions, sustained weight control, regular physical activity, smoking cessation and adoption of healthy diet habits are beneficial for the prevention and management of both diabetes and depression.

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