

Depression, Antidepressant Medication, and the Risk of Developing Type 2 Diabetes

a report by

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People who have diabetes are 1.5 to two times more likely to be depressed than people in the general population,¹ and depression in people with diabetes is associated with a range of poor outcomes, including higher blood glucose levels,² an increased risk of complication³ and mortality rates,⁴ and higher healthcare costs.⁵

Could Depression Increase the Risk of Developing Diabetes?

In 1674, Thomas Willis, the famous British physician who identified glycosuria as a sign of diabetes, was the first to address the natural history of comorbid depression and diabetes when he wrote that diabetes was caused by “sadness or long sorrow and other depressions.”⁶ For almost 300 years no-one pursued Willis’ provocative hypothesis, and when some researchers finally did search for what they called the ‘diabetogenic personality’ in people with type 1 diabetes, the search proved fruitless.^{7,8} At that point researchers turned from looking for the emotional causes of diabetes to looking for its emotional consequences. However, just over a decade ago research interest in Willis’ original idea was renewed, with fascinating results.

In 1996 Eaton and his colleagues at Johns Hopkins published a study suggesting that Willis might have been right after all, at least when it comes to a person’s risk of developing type 2 diabetes.⁹ This study was followed several years later by one conducted in Japan by Kawakami and colleagues.¹⁰ This study also supported Willis’ hypothesis. In each of these studies, and in the many that followed in the next 10 years, the researchers identified a group of people who at the outset of the study did not have diabetes and divided the group into those who were depressed and those who were not depressed. The researchers then followed their subjects for a certain period

of time (13 years in the Eaton study and eight years in the Kawakami study), and at the end of that period they compared the rates at which the originally depressed and ‘not depressed’ groups had developed diabetes.

Table 1 summarizes the studies designed to test Willis’ hypothesis.⁹⁻²² Not all of the studies fully supported the hypothesis, but most gave it at least some credence. Overall, these studies suggest that being depressed could increase a person’s risk of developing type 2 diabetes, although this effect could be limited to people in certain demographic groups (e.g. people under 50 years of age or those with less education), to people with high levels of depressive symptoms, or to people who are not already at a very high risk for developing diabetes. In the Diabetes Prevention Program (DPP), participants with elevated depression symptoms were not more likely to develop diabetes during the 3.2-year course of the study, perhaps because other diabetes risk factors might have overwhelmed the risk associated with depression.²¹

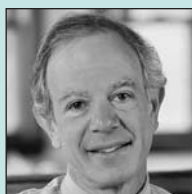
It is possible that some of these studies actually underestimate the effect of depression on diabetes risk. Some studies control for diabetes risk factors such as body mass index (BMI) and physical activity because they can be viewed as ‘confounders’ of depression’s effect on diabetes risk (i.e. as factors to be eliminated in order to obtain a more accurate estimate of the true effect of depression on diabetes risk). However, it is also possible to view factors such as BMI and physical activity as ‘mediators’ of depression’s effect on diabetes risk (i.e. as the mechanisms by which depression increases a person’s risk of developing diabetes). From this latter perspective depression might increase diabetes risk directly, or indirectly, by decreasing physical activity, and through other behaviors that increase BMI. Controlling for diabetes risk factors such as BMI and physical activity in studies can lead to underestimating the true effect of depression on diabetes risk.

How Could Depression Increase Diabetes Risk?

If depression does increase diabetes risk, it could have this effect via behavioral mechanisms, psycho-neurohormonal mechanisms, or both.

Behavioral Mechanisms

Depression is associated with a wide range of behaviors that are known diabetes risk factors, including physical inactivity, a higher BMI, smoking, and sleep disturbances. In the Women’s Health Study (WHS), BMI and physical inactivity were both independent risk factors for developing diabetes during the seven-year course of the study.²³ Several large randomized clinical trials have shown that decreasing BMI or increasing physical activity can reduce the risk of developing type 2 diabetes in those who are at high risk.²⁴⁻²⁶



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Dr Rubin’s publications are more than 100 papers, book chapters, abstracts, and articles on treatment adherence, the effects of diabetes education, psychological problems associated with diabetes, and techniques for counseling people with diabetes. He served as American Diabetes Association (ADA) President, Health Care and Education from July 2006 until June 2007, and is past Chair of the ADA Committee on Professional Councils and the Council on Behavioral Medicine and Psychology. Dr Rubin is also a former officer of the American Association of Diabetes Educators and former chair of the National Certification Board for Diabetes Educators.

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Table 1: Effect of Depression on Subsequent Risk of Developing Type 2 Diabetes

Study	Number of Subjects	Diagnostic Method	Duration of Follow-Up	Findings	Comments
East Baltimore Site of the Epidemiologic Catchment Area Survey (Eaton et al., 1996)	1,718 men and women	Diagnostic Interview (DIS)	13 years	RR: 2.23, 95% CI: 0.90–5.55	p=0.08
Kawakami et al., 1999	2,764 male employees	Zung Depression Screener	8 years	HR: 2.31, 95% CI: 1.03–5.20	p<0.05
Study of Women's Health Across the Nation (SWAN) (Everson-Rose et al., 2003)	2,254 pre-menopausal, middle-aged women	CES-D Depression Screener	2 years	OR: 2.28, 95% CI: 1.2–6.4 for African-Americans	p<0.30; too few cases in other ethnic groups for reliable assessment
National Health and Nutrition Examination Epidemiologic Survey Follow-Up Survey (NHEFS) (Carnethon et al., 2003)	6,190 men and women	General Well-Being Screener	>15 years	RR: 3.0, 95% CI: 2.0–4.7 for subjects with <HS education	RR is NSD for subjects with ≥HS education
NHEFS (Sadyah et al., 2003)	8,870 men and women	CES-D Depression Screener	9 years	RH: 1.11, 95% CI: 0.79–1.56	RH: 1.27 (95% CI: 0.93–1.73) not adjusting for BMI, physical activity
Nurses' Health Study (Arroyo, 2004)	72,178 female nurses	Mental Health Index Screener	4 years	RR: 1.2, 95% CI: 1.0–1.5	p=0.05
Atherosclerosis Risks in Communities (ARIC) Study (Golden et al., 2004)	11,615 men and women	Vital Exhaustion Screener	6 years	Highest quartile versus lowest RH: 1.38, 95% CI: 1.10–1.73	
Rancho Bernardo Study (Palinkas et al., 2004)	971 men and women	Beck Depression Inventory	8 years	OR: 2.50, 95% CI: 1.29–4.87	Type 2 diabetes at baseline not associated with later depression
Whitehall II Study (Kumari et al., 2004)	10,308 civil servants	General Health Questionnaire Depression Screener	12 years	OR (men): 1.17, 95% CI: 0.8–1.7; OR (women): 1.08, 95% CI: 0.6–1.9	OR for diabetes or IGT significant for men and women
Brown et al., 2005	1,622 men and women with diabetes, 2,279 without diabetes	Population-based, case-controlled administrative database	History of depression in previous 3 years	OR: 1.23, 95% CI: 1.10–1.37 for those 20–50 years of age	OR: 0.92, 95% CI: 0.84–1.00 for those ≥51 years of age
Engum, 2007	37,291 men and women	Population-based; Anxiety and Depression Index	10 years	OR (men): 1.48, 95% CI: 1.15–1.91 OR (women): 1.59, 95% CI: 1.24–2.04	OR for diabetes significant for men and women
The Cardiovascular Health Study (Carnethon et al., 2007)	4,681 adults ≥65 years of age	CES-D Depression Scale	10 years	HR: 1.6, 95% CI: 1.1–2.3	CES-D score increase HR: 1.5, 95% CI: 1.1–2.3
The Diabetes Prevention Program (DPP) (Rubin et al., 2008)	3,187 adults with 'pre-diabetes'	Beck Depression Inventory	3.2 years	HR not significant in any arm (placebo, metformin, lifestyle)	Antidepressant HR: 2.25, 95% CI: 1.38–3.66 in placebo arm HR: 3.48, 95% CI: 1.93–6.28 in lifestyle arm
Multi-Ethnic Study of Atherosclerosis (Golden et al., 2008)	5,201 adults without diabetes, 4,847 adults without depressive symptoms, some with diabetes	CES-D Depression Scale	3.2 years	HR: 1.10, 95% CI: 1.02–1.20 for every 5-point increase in CES-D score	For those with diabetes HR for elevated depression symptoms: 1.52, 95% CI: 1.09–2.12

Depression is also associated with smoking, another behavior known to increase a person's risk of developing diabetes. In the Insulin Resistance Atherosclerosis Study (IRAS), current smokers were almost three times as likely to develop diabetes over five years than those who had never smoked.²⁷ Depression is also associated with sleep disturbances, and some studies have found increased rates of diabetes in people who sleep either very little (less than five hours a night) or a lot (more than nine hours a night).^{28–30}

Psycho-neurohormonal Mechanisms

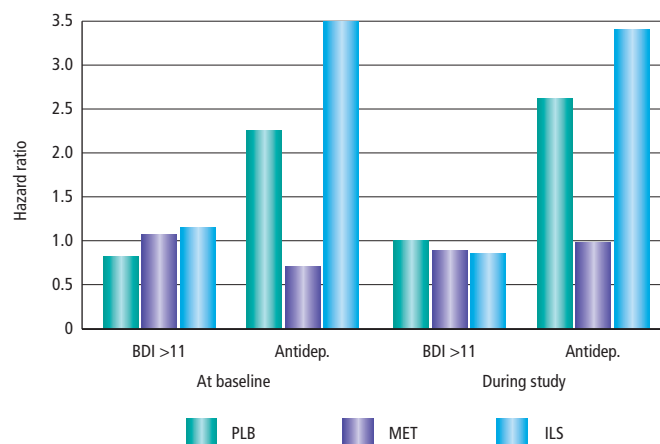
Depression could also increase diabetes risk via psycho-neurohormonal mechanisms and can be seen as a stress response 'gone awry.' Stress triggers release of catecholamines, growth hormone, glucagon, and cortisol, all of which increase blood glucose levels. When a person is depressed, this release is abnormally prolonged. Depression is also associated with the hypersecretion of pro-inflammatory cytokines, which may not only increase diabetes risk by interfering with insulin action, but

may also contribute to the risk of cardiovascular disease, the leading cause of death in people with diabetes.

Conclusions Regarding the Natural History of Depression and Type 2 Diabetes

There is ample evidence that being depressed may increase a person's risk of developing type 2 diabetes, at least for people who have high levels of depressive symptoms or for people who are not already at a very high risk for developing diabetes (as was the case for participants in the DPP). The fact that depression may be a risk factor for developing diabetes does not preclude the possibility that having diabetes could also increase a person's risk for being depressed. Diabetes-related distress, especially distress associated with diabetes complications, may increase depression risk.^{22,31} This may also, in part, explain the higher recurrence rates and longer duration of major depressive disorder (MDD) and depressive symptoms among those with diabetes compared with individuals who do not have diabetes.³²

Figure 1: Antidepressant Medication and Diabetes Risk in the Diabetes Prevention Program



Presented are data from the Diabetes Prevention Program (DPP) showing the association between elevated depression symptoms, antidepressant medication, and diabetes risk during the study. We see that elevated depression symptoms on entry to the study and during the study were not associated with increased diabetes risk in any DPP study arm. This finding contrasted with those from many of the studies mentioned earlier. This difference in findings could be explained by the much higher risk for developing diabetes in the DPP. Perhaps in this high-risk population the added risk associated with depression was overwhelmed by the risk associated with having impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) and being overweight. Antidepressant medication, on the other hand, was powerfully associated with increased diabetes risk among DPP participants in the placebo metformin (PLB) and intensive lifestyle program (ILS) arms, but not among those in the active metformin (MET) arm. DPP participants in the PLB or ILS arms who were taking antidepressants when they entered the study or who took them continuously during the study were two to three times more likely to develop diabetes during the study than participants in those arms that did not take antidepressants. Further research is needed to determine whether the association between antidepressant use and diabetes risk is the result of an independent contribution of these agents to diabetes risk or whether using these agents is a marker for more serious depression, or for chronic or recurrent depression.
Source: Rubin et al., Diabetes Care, 2008.

Depressive Symptoms, Antidepressant Use, and Diabetes Risk in the Diabetes Prevention Program

While a growing number of studies have assessed elevated depressive symptoms as a diabetes risk factor, very few have considered the association between antidepressant use and diabetes risk. The importance of examining the latter association is made clear by data from the DPP showing almost no overlap between individuals with elevated depressive symptoms and those taking antidepressant medication. On entry to the study, 10.3% of participants had elevated depressive symptom scores, 5.7% were taking antidepressants, and only 0.9% had elevated symptoms and were taking antidepressants. Since the vast majority of DPP participants taking antidepressants were taking them for depression rather than for other indications, it appears that almost all of those taking these agents were depressed individuals whose symptoms were effectively controlled with the medication.

This raises a critical question: should individuals whose depressive symptoms are controlled by medication be included in depression rate estimates? If the answer is yes, most studies, which base depression rates solely on the presence of elevated symptoms, may substantially underestimate the number of individuals who are truly depressed.

DPP participants were randomized to one of three treatment arms when they entered the study: an arm that took placebo metformin (PLB), an arm that took active metformin (MET), and an arm that was offered an intensive lifestyle program (ILS).

Data from the DPP strongly suggest that antidepressant use is a diabetes risk factor in individuals who are already at a very high risk for developing diabetes, while elevated depressive symptom scores were not associated with an increased diabetes risk (see Figure 1). When other factors associated with the risk of developing diabetes were controlled, neither elevated depressive symptom scores on entry to the study nor elevated scores during the study were associated with diabetes risk in any arm. Baseline antidepressant use was associated with diabetes risk in the PLB arm (hazard ratio [HR] 2.25, 95% confidence interval [CI] 1.38–3.65) and in the ILS arm (HR 3.48, 95% CI 1.93–6.28). Continuous antidepressant use during the study was associated with diabetes risk in the same arms (PLB: HR 2.60, 95% CI 1.37–4.94; ILS: HR 3.39, 95% CI 1.61–7.13), as was intermittent use during the study in the ILS arm (HR 2.07, 95% CI 1.18–3.62). Among MET arm participants, antidepressant use was not associated with developing diabetes.

These findings are striking, since they suggest that elevated depressive symptoms may not increase the diabetes risk in individuals who are already at very high risk for developing type 2 diabetes. Rates of developing diabetes in the DPP were five- to 10-fold higher than those in earlier studies where subjects did not necessarily have an impaired glucose tolerance at baseline. In addition, the DPP cohort was relatively free of depression. Perhaps in a population at a high risk for developing diabetes, generally mild symptoms of depression were not potent enough to significantly affect overall diabetes risk. This is consistent with the fact that some earlier studies found increased diabetes risk only in individuals with high levels of depression symptoms.³³

Antidepressant Use and Diabetes Risk

The DPP results are probably most notable for finding an increased diabetes risk in PLB and ILS participants who were taking antidepressant medication. Two recent studies also assessed the association between antidepressant use and diabetes risk. One study³⁴ found no significant association, but the study did not incorporate a definitive assessment of diabetes status. The other study³⁵ found an increased risk of developing diabetes among individuals taking selective serotonin re-uptake inhibitors (SSRIs) in addition to tricyclic antidepressants (TCA) compared with those taking TCA alone, but the study did not include individuals taking no antidepressants, so the authors could not assess the diabetes risk associated with taking any antidepressant.

In the DPP, 78% of those who were taking any antidepressant were taking SSRIs or related agents, which are generally considered to have less effect on weight than TCA, with some reports that SSRIs actually contributed to weight loss³⁶ and improved insulin sensitivity.³⁷ In the DPP, SSRI use was associated with minor weight gain, and use of these agents was associated with an increased diabetes risk in the PLB and ILS arms, which was the case for use of any antidepressant.

In an effort to explain the association between antidepressant use and diabetes risk we controlled all likely mediators, including fasting glucose level, weight on entry to the study, and weight gain during the study, but the association remained significant in the PLB and ILS arms. This left us without an explanation for the way in which antidepressant use increased diabetes risk, if it did at all. It is possible that antidepressant use is simply a marker for the actual cause or causes of increased diabetes risk. Perhaps antidepressant use is a marker for more severe depression in the past, or for recurrent depression. If so, the lingering effects of past depression, even with symptoms currently controlled by medication, could explain the association between

antidepressant use and diabetes risk. For this argument to hold, two things would have to be true. First, antidepressant users would have to suffer from past episodes of moderate to severe depression (or recurrent depression), and second, the effects of these episodes would have to operate after the symptoms had resolved, since DPP participants taking antidepressants did not have elevated symptoms on entry to the study or during the study. It is also possible that antidepressant users experience some effect of depression not detected by the questionnaire we used to assess depression.

Although there is no obvious explanation for the findings that antidepressant use was not associated with diabetes risk in the MET arm, the finding is similar to a previous DPP report that metformin treatment not only reduced the risk of developing diabetes compared with placebo treatment, but it also eliminated the predictive effect of BMI on diabetes risk.³⁸

Research Implications

The DPP finding of an association between antidepressant use and diabetes risk requires confirmation, ideally in studies examining the risk associated with different classes of antidepressant and even specific agents. These studies will require large populations to generate sufficient sample sizes; prescription databases could be one source. If these studies yield the same results as the DPP study, further studies should attempt to determine whether the use of these agents is an independent diabetes risk factor or whether antidepressant use is a marker for depression severity or chronicity. Studies comparing antidepressant-associated diabetes risk with psychotherapy-associated diabetes risk would also be useful.

Clinical Implications

If future studies show that antidepressant use is an independent diabetes risk factor, clinicians will need to keep this in mind when treating patients who are depressed and at high risk for developing diabetes. If some antidepressants are found to have relatively little risk of increasing rates of diabetes, these agents should be used rather than agents associated with higher diabetes risk. Psychological treatment could also help patients avoid the iatrogenic effects of antidepressants, although in many instances resources for such treatment are very limited. We do know that cognitive behavioral therapy, one form of psychological treatment for depression, was

Table 2: Two-item Depression Screener*

Over the last 2 weeks, how often have you been bothered by little interest or pleasure in doing things?

- Not at all (0)
- Several days (1)
- More than half the days (2)
- Nearly every day (3)

Over the last 2 weeks, how often have you been bothered by feeling down, depressed, or hopeless?

- Not at all (0)
- Several days (1)
- More than half the days (2)
- Nearly every day (3)

*Patients with a combined total score of 3 or more on the two questions could well be depressed, and further screening and assessment is warranted.

associated with improved glycemic control in patients who had high glycated hemoglobin (HbA_{1c}) levels.³⁹ This suggests a potential benefit for patients at risk of developing diabetes. Clinicians should also try to determine the depression status of patients who are at risk for developing diabetes, since many studies other than the DPP suggest that elevated symptoms are a diabetes risk factor. Likely depression status can be determined by asking patients questions about the two cardinal symptoms of depression. These questions and a scoring algorithm appear in *Table 2*. Patients with a combined total score of three or more on the two questions could well be depressed, and further screening and assessment is warranted.

Public Health Implications

Applying current estimates of the number of people in the US who have pre-diabetes (57 million with impaired glucose tolerance or impaired fasting glucose), and estimates of the prevalence of antidepressant use among adults in the US (at least 10%), it would seem that almost six million people in the US have pre-diabetes and are taking antidepressants. This is a fairly large number of people, and if future research confirms that antidepressants are an independent risk factor for type 2 diabetes, efforts to minimize the potentially negative effects of these agents on glycemic control should be pursued. The DPP findings suggest that the use of metformin might be beneficial. ■

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