# Depression in diabetes

**Calum D. Moulton MRCPsych[1,*], Khalida Ismail PhD[1]**

**[1] Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK**

***Corresponding author email: calum.moulton@kcl.ac.uk**

## Abstract

Depression is twice as common in patients with diabetes; it is associated with an increased risk of diabetes complications and premature mortality. However, the mechanisms linking the two conditions are poorly understood and current treatments for depression frequently fail to improve diabetes outcomes. In addition to shared psychological factors, there is increasing evidence that biological mechanisms, such as elevated inflammation, may contribute to a common underlying mechanism for depression and type 2 diabetes. Improved understanding of such mechanisms has identified novel targets for treatment that may improve depression and diabetes simultaneously. In the longer term, such pathways may provide targets to prevent the onset of type 2 diabetes in depression altogether.

## 1. Introduction

Patients with diabetes are twice as likely to suffer from depression, a relationship seen for both type 1 diabetes and type 2 diabetes (1). Compared to those with diabetes alone, patients with comorbid depression experience poorer quality of life, increased risk of diabetes complications and premature mortality (2-4). As the worldwide incidence of diabetes continues to rise, delineating the mechanisms linking depression and diabetes proves ever more important. In addition to psychological and behavioural factors, there is mounting evidence that shared biological mechanisms may lead to both depression and diabetes, providing novel treatment targets and even opportunities for primary prevention. Focussing on type 2 diabetes, this review briefly summarises the epidemiology and mechanisms of the link between depression and diabetes, before scrutinising a range of possible treatments, including current and novel therapies.

## 2. Depression in type 1 diabetes

Type 1 diabetes (T1D) and type 2 diabetes (T2D) can be regarded as distinct conditions. In contrast to T2D, which is typically diagnosed in mid-adult life and can often be managed with lifestyle modification or tablet therapies, T1D necessitates life-long insulin injections and is usually diagnosed during adolescence or young adulthood. Unlike T2D, this means that the average age of onset of T1D precedes that of depression (5). Collectively, these factors suggest that different mechanisms may underlie the respective relationships between depression and both T1D and T2D. For T1D, these mechanisms are incompletely understood but may include psychological maladjustment to T1D, fear of hypoglycaemia, interpersonal difficulties and even biological mechanisms. Because T2D is 10 times more common and more extensively researched in relation to depression than T1D, the remainder of this review discusses T2D alone. More extensive reviews of depression in T1D have been published (6).

## 3. Depression in type 2 diabetes: overview

### *3.1 Definition of depression*

Prevalence estimates of depression in T2D have varied between 10 and 20%, around twice that of the general population (1). A higher prevalence is generally reported when depression is assessed by self-report questionnaires rather than by using diagnostic interview (7). However, there is evidence that 'subthreshold' depressive symptoms may predict poor long-term outcomes in T2D (8). Because of this, the current review will include papers that define depression according either to diagnostic criteria or to self-report questionnaire measures with a validated cut-off score.

*3.2 Complications of depression in T2D*

There is consistent evidence that patients with depression and T2D are at increased risk of microvascular complications (such as retinopathy and neuropathy), macrovascular complications (such as stroke and heart attack) and premature mortality (2, 3). In addition, depression is associated with a two-fold increase in the risk of dementia in T2D (9, 10). Understanding the underlying mechanisms is therefore crucial in targeting strategies to prevent adverse outcomes in patients with depression and T2D.

## 4. Mechanisms of depression in T2D

*4.1 Psychological mechanisms*

The traditional explanation for the link between depression and T2D has been the psychological model. In such a model, the burden of living with a chronic disorder predisposes to depression, which in turn leads to worsening diabetes self-care and increased risk of diabetes complications (6). Depression in T2D is associated with poorer diet and concordance with diabetes treatment (11).

Increasingly, however, limitations of the psychological model have become apparent. Despite a modest cross-sectional association (12), depression is at best weakly associated with worsening of glycaemic control over time (13, 14). Moreover, the link between depression and T2D is bidirectional: whilst diabetes increases the risk of incident depression by around 20%, depression increases the risk of incident diabetes by up to 60% (15, 16). This suggests a more complex relationship between depression and T2D.

*4.2 Biological mechanisms*

There is striking overlap between depression and T2D in their associated brain changes (17), suggesting shared biological mechanisms. Several such mechanisms have been proposed for the association between diabetes and depression throughout the life course, summarised below.

*4.2.1 Genetic and epigenetic links*

Whereas a study of 17,404 people at risk for T2D found no genetic associations between depression and T2D (18), a more recent Danish twin study found that genetic effects accounted for the majority of the covariance observed (19). Future genome-wide association studies are needed to address these inconsistencies.

*4.2.2 Inflammation*

Elevated inflammation is strongly implicated in the pathogenesis of both depression (20) and T2D (21) respectively, as well as in the pathogenesis of macrovascular complications (22). In diabetes, anti-inflammatory treatments have been found to improve glycaemic control (23), and anti-inflammatory treatments may improve depression in the general population (24). In the South London Diabetes cohort of 1790 people with newly-diagnosed T2D, patients with depression were found to have elevated concentrations of several inflammatory markers compared to non-depressed controls, even after controlling for potential confounders (25). This suggests that an elevated inflammatory response may be an important mediator of the depression in T2D and of its associated adverse outcomes. The elevated inflammation may occur as a result of shared stressors throughout the life course, including childhood abuse, work stress and obesogenic lifestyles (6).

*4.2.3 Hypothalamic-pituitary-adrenal (HPA) axis*

Chronic dysregulation of the HPA axis has been implicated in the pathogenesis of depression (26) and T2D (27) respectively. Early stress has been found to lead to attenuated hippocampal development (28); the hippocampus is an area with a high density of glucocorticoid receptors and the latter are strongly implicated in both depression and T2D. A study of patients with coronary heart disease found that those with depression had reduced glucocorticoid receptor expression and sensitivity, as well as elevated concentrations of inflammatory markers (29). Research defining the directionality of such relationships, as well as research specifically in the comorbid depression and T2D population, is now awaited.

## 5. Treatments for depression in T2D

*5.1 Current treatments*

There is good evidence that antidepressant medications, including selective serotonin reuptake inhibitors, bring about significant short-term and longer-term improvements in depression in patients with T2D (30, 31). Cognitive behavioural therapy has also been used to treat depression in T2D, producing positive effects on depressive symptoms (32), albeit not always sustained (33). For both pharmacological and psychological therapy, however, improvements in depression do not consistently translate into improvements in glycaemic control (34, 35), whilst data on long-term complications such as cardiovascular disease are lacking. A systematic review of collaborative interventions in patients with diabetes found a significant overall improvement in both depression and glycaemic control (36). However, depression remission did not predict better glycaemic control across studies, again suggesting a more complex relationship between the two conditions.

*5.2 Novel treatments*

Given the limitations identified in treating depression in isolation, therapies that treat depression and diabetes simultaneously are warranted. Both psychological and pharmacological approaches have such potential, and lifestyle interventions to address social interaction, inactivity, diet, smoking and alcohol use may also lead to improvements in both depression and diabetes (37). Recent epidemiological research has suggested that depression can be divided into different subtypes with different longer-term prognoses (38, 39), and better identification of such subtypes may reduce treatment failure.

In contrast to the large number of psychological and complex intervention studies ongoing in the field of depression in T2D (35), studies of pharmacological agents are scarce. This is surprising given their promise in observational research.

In the South London Diabetes study, patients prescribed incretin-based diabetes treatments, which have potent anti-inflammatory properties, were found to improve in terms of depressive symptoms over time, compared to patients receiving other therapies (40). This improvement correlated with reduction in inflammation but not HbA1c, suggesting that inflammation may be an effective target for the treatment of depression in T2D. However, no previous clinical trial has attempted to reduce inflammation in the treatment of both depression and T2D.

Modification of the HPA axis provides another target for shared treatment of depression and T2D, although no studies have yet attempted such treatment in this comorbid population.

## 6. Future directions

A major limitation of current therapy for depression in T2D has been the failure to improve long-term diabetes outcomes in this high-risk group. One explanation is the lack of precision in the definition of depressive illness in T2D, leading to 'one size fits all' treatments. Future research should therefore investigate whether distinct subtypes of depression can be more clearly phenotyped, both psychologically and biologically, in order to target precision treatments. The limitations of current treatments may also reflect their failure to modify underlying biological processes, which therefore continue unabated in driving adverse diabetes outcomes. Through advances in basic science, neuroimaging and prospective epidemiological research, better identification of the shared origins of depression and T2D could identify targets for disease-modifying therapies that bring about long-term benefits. For example, reduction in inflammation could lead to improvements in depression, glycaemic control and subsequent cardiovascular disease risk. Whilst research into the T2D population continues, future research must also focus on the longitudinal relationship between depression and pre-diabetes stages. Better understanding of these mechanisms may provide opportunities to delay the onset of diabetes, or even prevent it altogether. As the prevalence of T2D rises inexorably, research into such preventative interventions is urgently needed.

## References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001 Jun 1;24(6):1069-78.

2. De Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosomatic Medicine. 2001 Jul 1;63(4):619-30.

3. Katon WJ, Rutter C, Simon G, Lin EH, Ludman E, Ciechanowski P, Kinder L, Young B, Von Korff M. The association of comorbid depression with mortality in patients with type 2 diabetes. Diabetes Care. 2005 Nov 1;28(11):2668-72.

4. Carper MM, Traeger L, Gonzalez JS, Wexler DJ, Psaros C, Safren SA. The differential associations of depression and diabetes distress with quality of life domains in type 2 diabetes. Journal of Behavioral Medicine. 2014 Jun 1;37(3):501-10.

5. Kessler RC, Amminger GP, Aguilar-Gaxiola S, Alonso J, Lee S, Ustun TB. Age of onset of mental disorders: a review of recent literature. Current Opinion in Psychiatry. 2007 Jul;20(4):359.

6. Moulton CD, Costafreda SG, Horton P, Ismail K, Fu CH. Meta-analyses of structural regional cerebral effects in type 1 and type 2 diabetes. Brain Imaging and Behavior. 2015 Dec 1;9(4):651-62.

7. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. The Lancet Diabetes & Endocrinology. 2015 Jun 1;3(6):450-60.

8. Schmitz N, Gariépy G, Smith KJ, Clyde M, Malla A, Boyer R, Strychar I, Lesage A, Wang J. Recurrent subthreshold depression in type 2 diabetes: an important risk factor for poor health outcomes. Diabetes Care. 2014 Apr 1;37(4):970-8.

9. Katon W, Lyles CR, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of depression with increased risk of dementia in patients with type 2 diabetes: the Diabetes and Aging Study. Archives of General Psychiatry. 2012 Apr 1;69(4):410-7.

10. Sullivan MD, Katon WJ, Lovato LC, Miller ME, Murray AM, Horowitz KR, Bryan RN, Gerstein HC, Marcovina S, Akpunonu BE, Johnson J. Association of depression with accelerated cognitive decline among patients with type 2 diabetes in the ACCORD-MIND trial. JAMA Psychiatry. 2013 Oct 1;70(10):1041-7.

11. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. Diabetic Medicine. 2015 Jun;32(6):725-37.

12. Lustman PJ, Anderson RJ, Freedland KE, De Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care. 2000 Jul 1;23(7):934-42.

13. Fisher L, Mullan JT, Arean P, Glasgow RE, Hessler D, Masharani U. Diabetes distress but not clinical depression or depressive symptoms is associated with glycemic control in both cross-sectional and longitudinal analyses. Diabetes Care. 2010 Jan 1;33(1):23-8.

14. Palta P, Golden SH, Teresi JA, Palmas W, Trief P, Weinstock RS, Shea S, Manly JJ, Luchsinger JA. Depression is not associated with diabetes control in minority elderly. Journal of Diabetes and its Complications. 2014 Nov 1;28(6):798-804.

15. Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, Pouwer F. European Depression in Diabetes (EDID) Research Consortium. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia. 2010;53(12):2480-6.

16. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care. 2008 Dec 1;31(12):2383-90.

17. Cole J, Costafreda SG, McGuffin P, Fu CH. Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. Journal of Affective Disorders. 2011 Nov 1;134(1-3):483-7.

18. Samaan Z, Garasia S, Gerstein HC, Engert JC, Mohan V, Diaz R, Anand SS, Meyre D. Lack of association between type 2 diabetes and major depression: epidemiologic and genetic evidence in a multiethnic population. Translational Psychiatry. 2015 Aug;5(8):e618.

19. Kan C, Pedersen NL, Christensen K, Bornstein SR, Licinio J, MacCabe JH, Ismail K, Rijsdijk F. Genetic overlap between type 2 diabetes and depression in Swedish and Danish twin registries. Molecular Psychiatry. 2016 Jul;21(7):903.

20. Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatry. 2014 Oct 1;71(10):1121-8.

21. Pickup JC, Crook MA. Is type II diabetes mellitus a disease of the innate immune system? Diabetologia. 1998 Sep 1;41(10):1241-8.

22. Pickup JC, Mattock MB. Activation of the innate immune system as a predictor of cardiovascular mortality in type 2 diabetes mellitus. Diabetic Medicine. 2003 Sep;20(9):723-6.

23. Goldfine AB, Fonseca V, Jablonski KA, Chen YD, Tipton L, Staten MA, Shoelson SE. Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. Annals of Internal Medicine. 2013 Jul 2;159(1):1-12.

24. Na KS, Lee KJ, Lee JS, Cho YS, Jung HY. Efficacy of adjunctive celecoxib treatment for patients with major depressive disorder: a meta-analysis. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2014 Jan 3;48:79-85.

25. Laake JP, Stahl D, Amiel SA, Petrak F, Sherwood RA, Pickup JC, Ismail K. The association between depressive symptoms and systemic inflammation in people with type 2 diabetes: findings from the South London Diabetes Study. Diabetes Care. 2014 May 14:DC_132522.

26. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. Psychosomatic Medicine. 2011 Feb 1;73(2):114-26.

27. Rosmond R, Björntorp P. The hypothalamic–pituitary–adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. Journal of Internal Medicine. 2000 Feb;247(2):188-97.

28. Teicher MH, Andersen SL, Polcari A, Anderson CM, Navalta CP, Kim DM. The neurobiological consequences of early stress and childhood maltreatment. Neuroscience & Biobehavioral Reviews. 2003 Mar 31;27(1):33-44.

29. Nikkheslat N, Zunszain PA, Horowitz MA, Barbosa IG, Parker JA, Myint AM, Schwarz MJ, Tylee AT, Carvalho LA, Pariante CM. Insufficient glucocorticoid signaling and elevated inflammation in coronary heart disease patients with comorbid depression. Brain, Behavior and Immunity. 2015 Aug 1;48:8-18.

30. Lustman PJ, Clouse RE, Nix BD, Freedland KE, Rubin EH, McGill JB, Williams MM, Gelenberg AJ, Ciechanowski PS, Hirsch IB. Sertraline for prevention of depression recurrence in diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Archives of General Psychiatry. 2006 May 1;63(5):521-9.

31. Echeverry D, Duran P, Bonds C, Lee M, Davidson MB. Effect of pharmacological treatment of depression on A1C and quality of life in low-income Hispanics and African Americans with diabetes: a randomized, double-blind, placebo-controlled trial. Diabetes Care. 2009 Dec 1;32(12):2156-60.

32. Hermanns N, Schmitt A, Gahr A, Herder C, Nowotny B, Roden M, Ohmann C, Kruse J, Haak T, Kulzer B. The effect of a diabetes-specific cognitive behavioral treatment program (DIAMOS) for patients with diabetes and subclinical depression: results of a randomized controlled trial. Diabetes Care. 2015 Jan 7:dc141416.

33. Safren SA, Gonzalez JS, Wexler DJ, Psaros C, Delahanty LM, Blashill AJ, Margolina AI, Cagliero E. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in patients with uncontrolled type 2 diabetes. Diabetes Care. 2014 Mar 1;37(3):625-33.

34. Katon WJ, Von Korff M, Lin EH, Simon G, Ludman E, Russo J, Ciechanowski P, Walker E, Bush T. The pathways study: A randomized trial of collaborative care in patients with diabetesand depression. Archives of General Psychiatry. 2004 Oct 1;61(10):1042-9.

35. Petrak F, Baumeister H, Skinner TC, Brown A, Holt RI. Depression and diabetes: treatment and health-care delivery. The Lancet Diabetes & Endocrinology. 2015 Jun 1;3(6):472-85.

36. Atlantis E, Fahey P, Foster J. Collaborative care for comorbid depression and diabetes: a systematic review and meta-analysis. BMJ Open. 2014 Apr 1;4(4):e004706.

37. Sarris J, O'Neil A, Coulson CE, Schweitzer I, Berk M. Lifestyle medicine for depression. BMC Psychiatry. 2014 Dec;14(1):107.

38. Harald B, Gordon P. Meta-review of depressive subtyping models. Journal of Affective Disorders. 2012 Jul 1;139(2):126-40.

39. Bruce DG, Davis WA, Dragovic M, Davis TM, Starkstein SE. Comorbid anxiety and depression and their impact on cardiovascular disease in type 2 diabetes: the Fremantle Diabetes Study phase II. Depression and Anxiety. 2016 Oct;33(10):960-6.

40. Moulton CD, Pickup JC, Amiel SA, Winkley K, Ismail K. Investigating incretin-based therapies as a novel treatment for depression in type 2 diabetes: Findings from the South London Diabetes (SOUL-D) Study. Primary Care Diabetes. 2016 Apr 1;10(2):156-9.