Diabetes and Depression – A Burdensome Co-morbidity

a report by

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Diabetes and Depression

Depression is a frequent co-morbid condition in people with diabetes. A meta-analysis of 42 studies demonstrated that 31% of patients with diabetes described themselves as having elevated depressive symptoms compared with 14% of those without diabetes. A clinical depression diagnosis based on standardised criteria defined by the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) or the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) occurred in 11.4% of patients with diabetes, whereas the prevalence in people without diabetes was 5%.[1] In clinical care settings this means that out of 100 patients with diabetes, approximately 11–12 meet the diagnostic criteria for clinical depression and another 20 have mild or subthreshold depression. Thus, approximately every third patient with diabetes is affected by depression or elevated depressive symptoms. The reasons for this close association between diabetes and depression are not yet fully understood. Below we will discuss three possible explanations.

First, diabetes could be a consequence of depression. This was first suggested 300 years ago by the British physician Thomas Willis, who thought that diabetes might be a consequence of prolonged sorrows.[2] In more recent years this historical observation has been supported by growing empirical evidence. A meta-analysis showed that the presence of depressive symptoms increased the risk of developing diabetes by 37%.[3] The reason for this timely relationship between depression and diabetes manifestation is unclear. It could be that people with elevated depressive symptoms are less attentive towards a healthy lifestyle, therefore increasing their risk for type 2 diabetes. Alternative explanations for this finding refer to chronic dysregulations of the hypothalamic–pituitary–adrenal (HPA) axis such as high cortisol levels and reduced insulin sensitivity or an activation of the immune system leading to or fostering chronic inflammatory processes[4] (see *Figure 1*). A second explanation for the close relationship between depression and diabetes comes from the observation that depressed patients with diabetes also report a high amount of diabetes-related distress.[5,6] In a clinical survey, only 14.7% of patients with low or no depression reported a high amount of diabetes-related distress. However, 56.3% of patients with mild depression and 73.6% with more severe clinical depression suffered from diabetes-related distress.[6] It might be that in vulnerable patients a high amount of diabetes-related distress or a deficit in coping with diabetes-related problems could result in elevated depression symptoms. A third explanation stems from study results indicating that blood glucose is itself a potent regulator for mood states. In particular, hypoglycaemia or severe hyperglycaemia are able to induce negative emotional states in patients with diabetes.[7–9]

It may be that these three possible explanations for the close association between diabetes and depression are not exclusive. While the understanding of the causes for the high co-morbidity of diabetes and depression clearly needs further research, there is cumulating evidence about the negative sequelae of depression in diabetes.

Depression and Quality of Life

An optimal quality of life is one of the primary objectives of diabetes therapy. Depression in diabetes impairs quality of life in patients with diabetes. In an Australian survey, depression was associated with poorer quality of life in all eight quality of life dimensions (physical functioning, role limitations due to impaired physical health, bodily pain, general health, vitality, social functioning, role limitations due to impaired emotional health and mental health) in patients with diabetes.[10] A recently published World Health Organization (WHO) World Health Survey about the impact of depression on quality of life in different chronic diseases (arthritis, asthma, angina and diabetes) showed that quality of life was most impaired in patients with diabetes and depression.[11]

Self-care Behaviour

The co-morbidity of depression and diabetes has also been taken seriously because of their implications for diabetes self-care behaviour.[12,13] There is evidence that depression might be a barrier to effective diabetes self-care. Patients with diabetes with a higher depression score showed higher rates of non-adherence to oral antidiabetes medication, took part in less exercise and showed more unhealthy dietary behaviour and less glucose monitoring. More complex self-care behaviours such as achieving and maintaining lifestyle changes were more strongly affected by depression than less complex self-care behaviours such as adherence to medication (see *Figure 2*). These findings have been reconfirmed by a current meta-analysis by Gonzales and colleagues[14] In line with these findings are the results of a meta-analysis of the association between depression and glycaemic control.

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Figure 1: Possible Physiological Pathways Linking Depression and Psychological Stress to Pathophysiology of Diabetes[4]

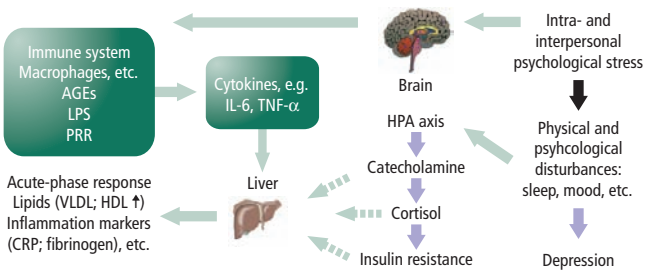


Figure 2: Impact of Depression on Diabetes Self-management[12]

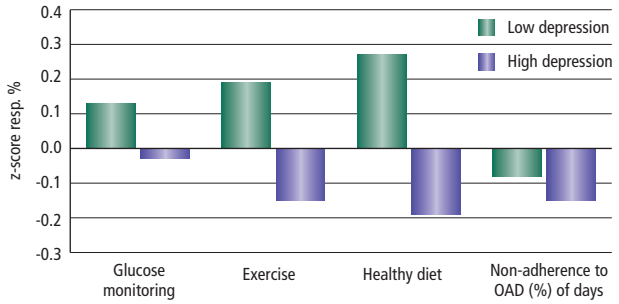
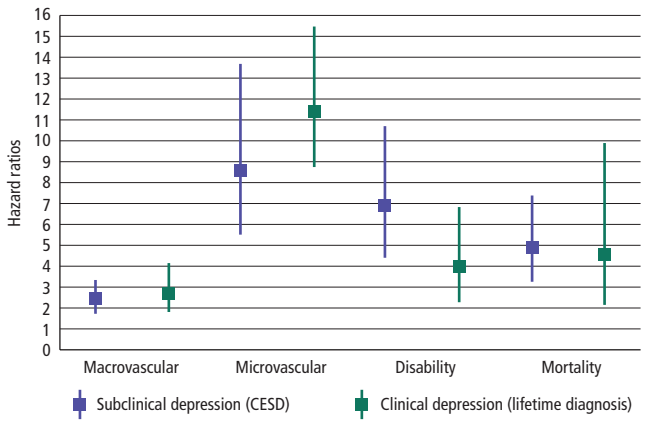


Figure 3: Impact of Subthreshold and Clinical Depression on Prognosis of Diabetes[16]



There was a significant correlation between depression and poor glycaemic control. In patients with diabetes a worse depression score was seen with poorer glycaemic control.[15]

Prognosis of Diabetes

Depression in people with diabetes is also a risk factor for the occurrence of late complications and functional disabilities. In a prospective study with a seven-year follow-up, Black and colleagues demonstrated that the hazard ratio for macrovascular complications was more than three times higher if depressive symptoms were present in patients with diabetes at baseline. For microvascular complications and functional disability, minor depression was a risk factor associated with a hazard ratio of 8.6 and 6.9, respectively. The difference between mild and more severe depression with regard to the risk of late complications was surprisingly rather small[16] (see *Figure 3*). Thus, it seems that even milder forms of depression must be taken seriously.

An epidemiological analysis of the National Health and Nutrition Examination Survey (NHANES) also revealed that depression is a risk factor for enhanced mortality in patients with diabetes. Mortality was 54% higher in depressed patients with diabetes compared with non-depressed patients.[17,18] Katon and colleagues found a hazard rate for mortality of 1.67 in patients with diabetes and minor depression, whereas this relative risk rose to 2.67 in patients with diabetes and major depression.[19]

Socioeconomic Aspects of Depression in Diabetes

Depression in diabetes has also socioeconomic implications. Individuals with diabetes and co-morbid depression have higher odds of functional disability compared with individuals with either diabetes or major depression alone. Depression in individuals with diabetes is associated with an increased disability burden, lost productivity and increased healthcare use and expenditures. In spite of poorer outcomes, costs associated with the treatment of depressed patients with diabetes are 60–80% higher than in non-depressed patients with diabetes.[20–22] Depression in diabetes should be taken seriously because of the negative impact on quality of life, diabetes self-management and the long-term prognosis of diabetes and elevated health expenditures.

Treatment of Depression in Diabetes

The adverse consequences of depression in diabetes are avoidable since depression in diabetes is a treatable condition. There are two treatment options. As a rather unspecific intervention, diabetes education has proved to be effective in reducing depression levels in patients with diabetes. More specific interventions for the treatment of depression in patients with diabetes are antidepressive pharmacological or psychotherapeutic interventions.

Diabetes Education

Diabetes education is effective in reducing subthreshold depression. Peyrot and Rubin observed a reduction of the rate of subthreshold depression six months after diabetes education from 38 to 13%.[23] Another study observed a reduction of subthreshold depression from 28 to 18% one year after diabetes education in a group setting and from 34 to 17% after diabetes education comprising individual counselling.[24] However, diabetes education has also been found to be effective in more severe cases of clinical depression. Diabetes education was frequently used as a 'placebo treatment' in randomised controlled trials comparing diabetes education with more specific antidepressive treatments such as nortriptyline, fluoxetine or cognitive behaviour therapy in patients with diabetes with major or clinical depression. The remission rate of major depression after diabetes education, which served as a control condition, was between 35 and 40%.[25–27] Diabetes education has the ability to halve the rate of subthreshold depression and even reduce the rate of major depression by more than one-third. Diabetes education enhances knowledge about diabetes and improves coping skills with the challenges of the disease, and could result in higher perceived control over the illness and fewer feelings of being helpless or overwhelmed by the disease.

Specific Antidepressive Interventions

More specific antidepressive treatments are antidepressive medication and psychotherapy. The effects of the antidepressive drugs nortriptyline[25] and fluoxetine[27] have been studied in patients with diabetes. Both substances are able to create a remission of major depression in more than 50% of cases. In another study, Lustman and colleagues found that maintenance therapy with sertraline was effective in preventing the recurrence of depression in patients with diabetes. The time until recurrence of depressive episode was 226 days in the sertraline group and 57 days in the control group receiving placebo.[28]

The effect of cognitive behaviour therapy has been studied as a psychotherapeutic method. Cognitive behaviour therapy focuses on the change of dysfunctional attitudes and negative cognitions of the patient with diabetes and replaces these with more appropriate perspectives and cognitions. In one study cognitive behaviour therapy led to a remission rate of major depression of 70%.[26] Thus, all specific antidepressive treatment was effective in reducing depression in patients with diabetes, but only cognitive behaviour therapy also led to an improvement of glycaemic control.[26] Fluoxetine[27] had no additional beneficial effect on glycaemic control whereas nortriptyline treatment led to a slight deterioration of glycaemic control after eight weeks.[25] Paroxetine also showed a slight improvement of glycaemic control after three months. However, this effect was not statistically significant after six months.[29]

Although there is evidence for the efficacy of antidepressive treatment in patients with diabetes, one problem is that the research focused on antidepressive treatment was conducted in rather small samples (<100 subjects) and rather short follow-up periods (<12 months) now. Thus, there is an urgent need for larger treatment studies and longer follow-up periods for the evaluation of antidepressive therapy in patients with diabetes. There is evidence that depression in diabetes is not an inevitable fate leading to a poor prognosis and reduced quality of life, but it can be effectively treated.

Screening for Depression

Nevertheless, since subthreshold as well as clinical depression is a treatable condition in diabetes, there is a great change for the effective management of depression in diabetes care. A prerequisite for an effective management of depression in diabetes care is a timely recognition of depressed mood in patients with diabetes. A big barrier is a rather disappointingly low recognition rate of depression in clinical settings. Studies indicate a detection rate of depression in primary care of 25–30%.[30–32] The timely identification of depressed patients with diabetes seems to be a great challenge in routine diabetes care, therefore regular screening for depression is requested by several guidelines.[33–36]

Screening Tools

Screening tools for depression in diabetes should be simple, have sufficient screening performance and be acceptable to both healthcare professionals and patients.[37] The current risk of a patient with diabetes suffering from depression can be assessed by the presence or absence of well-known risk factors for depression in diabetes. Elevated depression levels are found in patients with diabetes who are female, live alone, suffer from late or acute complications and who experienced a critical life event in the past or had poor glycaemic control.[38,39] Besides the appraisal of risk factors, two verbal screening questions have proved to be effective in detecting unrecognised depression in primary care settings: "During the past month have you often been bothered by feeling down, depressed or hopeless?" and "During the past month have you often been bothered by little interest or pleasure in doing things?"[40]

For more structured depression screening there are several validated questionnaires available. In general, all depression scales used to screen for depression or to assess depressive symptoms in the general population could be used for diabetes. Specific evidence about the screening performance of questionnaires in patients with diabetes is available for the Beck Depression Inventory (BDI),[6,41] the Centre of Epidemiological Studies Depression Scale (CES-D)[6] and the Patient Health Questionnaire (PHQ 9).[13]

Table 1: Performance of Screening Tools

Screening Tool	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
BDI	90	84	59	97
BDI	87	81	66	83
CES-D	79	89	54	96
PHQ-9	61	94	66	94
WHO 5	100	78	45	100
PAID	81	74	34	96
2 screening questions	97	67	18	99

BDI = Beck Depression Inventory ; CES-D = Center for Epidemiologic Studies Depression Scale; PHQ-9 = nine-item Patient Health Questionnaire; WHO 5 = World Health Organization (WHO) Five Wellbeing Index; PAID = Psychometric evaluation of the Problem Areas in Diabetes.

The WHO 5 questionnaire[42] and the Problem Areas in Diabetes questionnaire (PAID)[6] were also used for depression screening in patients with diabetes. The latter two questionnaires are measuring a broader aspect of negative emotional status in patients with diabetes (psychological wellbeing, diabetes-related distress) than the more specific depression questionnaire. The screening performance of questionnaires is evaluated according to their sensitivity and specificity as well as their positive and negative predictive values. *Table 1* summarises the screening performance of the above-mentioned screening instruments.

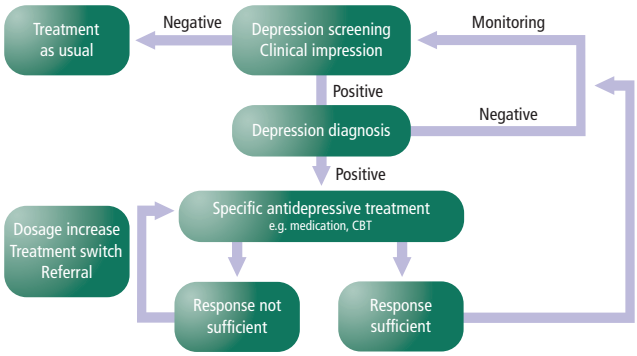
Depression questionnaires such as the BDI and CES-D showed high sensitivity and specificity. Positive predictive values were higher than 50% and negative predictive values were also good. The questionnaires that are less depression-specific such as the WHO 5 and the PAID had a similar sensitivity to depression questionnaires but a lower specificity. The lower specificity may be caused by the fact that these questionnaires measure more emotional aspects (psychological wellbeing and diabetes-related distress). Therefore, positive predictive values were lower than 50%.

The advantage of questionnaire-based depression screening tools is that they are easy to administer and evaluate. Depression questionnaires are able not only to screen for clinical depression but also to identify subthreshold emotional problems. Questionnaires asking about diabetes-related distress or general wellbeing might be better accepted by patients with diabetes seeking medical treatment because they may expect to be asked about diabetes-related problems or wellbeing instead of depressed feelings and suicidal intentions. However, this advantage is balanced by a somewhat lower screening performance of these less depression-specific questionnaires. The relatively smaller screening performance of verbal questions may be explained by a varying readiness for patients to speak about emotional problems. In summary, there are various screening tools with sufficient screening performance available that are also able to fit into different clinical settings.

Depression Management in Diabetes Care

Depression management programmes for patients with diabetes should prove that they are able to reduce the incidence and prevalence of depression in diabetes and that they are cost-effective in the long term.[43,44] Until now, there have been no meta-analytic findings based on randomised controlled trials about the effectiveness of depression screening in diabetes. Therefore, we have to rely on a Cochrane review about the efficacy of depression screening in primary care settings, in which most patients with diabetes are treated. The Cochrane review by Gilbody extended the scope of review to the effect of depression screening programmes towards the

Figure 4: Stepped Care Approach in the Management of Depression in Diabetes



impact on the management of depression in primary care settings.[45] Depression screening is able to identify unrecognised cases. Screening measures increased the detection rate of depression in primary care settings for approximately 30%, but surprisingly depression management in patients participating in screening programmes was not significantly better than for the unscreened control group.[45] Thus, screening without a structured approach for the management of depression seems to have no substantial impact on depression in primary care settings.

The successful management of depression in diabetes care settings requires a structured procedure consisting of screening for depression, verification of depression diagnosis, treatment of depression and evaluation of the treatment response on depression (see *Figure 4*).

The Pathway Study is a very promising example of a comprehensive approach to an improved management of depression.[13] In this approach patients with diabetes in the Seattle area were screened for depression using the PHQ-9. A positive screening result was confirmed using the Hopkins Symptom Checklist. Depressed patients with diabetes were offered a choice of antidepressive medication or problem-solving therapy. If depression was persistent after 10–12 weeks, the initial treatment was either intensified or switched (from drugs to problem-solving therapy and vice versa). If depressed patients with diabetes did not respond to the intensification or treatment switch, they were referred to a specialised mental health service. This approach was compared with controls in a randomised trial. Members of the control group were informed that they have a depression and were asked to speak with their primary care physician about depression treatment. There was a significant effect in favour of the stepped-care approach, which reduced depression by 40%, compared with the control group, which reduced depression by 12%. This study showed that a structured stepped-care approach containing screening, the offer of treatment options and an assessment of treatment response has the potential to reduce depression in diabetes effectively.

Cost-effectiveness of Managing Depression in Diabetes

In the face of finite healthcare resources, the cost-effectiveness of depression screening in diabetes is of course a matter of debate. In the Pathways Study, a cost-effectiveness analysis was performed.[46] This analysis showed that within two years an increase of days without depression to 61 days per patient and year was achieved. The cost-analysis showed that, while controlling for various confounding variables, the above-described stepped care approach led to a net cost reduction of US$314 in total healthcare costs per year. These healthcare costs also cover additional costs for depression screening (US$27) and antidepressive treatment (US$545). These are promising results showing that the implementation of depression screening within a stepped care approach is effective with regard to depression but also with regard to cost-effectiveness.

Conclusions

Depression in diabetes has a negative impact on diabetes self-care, quality of life and long-term prognosis. A timely identification of patients with subthreshold or clinical depression and a structured approach for the management of depression in diabetes has proved to be effective in reducing the burden of depression in diabetes. In the short term, healthcare expenditure can be saved. In the long term, a better prognosis, maintenance or improvement in quality of life can be achieved in patients with diabetes, which is the ultimate goal of diabetes therapy. ■

1. Anderson RJ, Freedland KE, Clouse RE, *Diabetes Care*, 2001;24(6):1069–78.
2. Willis T, *Pharmaceutice rationalis sive diabtriba de medicamentorum operantionibus in humano corpore*, MDCLXXV, Oxford, 1675.
3. Knol MJ, Twisk JW, Beekman AT, et al.,*Diabetologia*, 2006;49(5):837–45.
4. Pickup JC, *Diabetes Care*, 2004;27(3):813–23.
5. Fisher L, Skaff MM, Mullan JT, et al., *Diabetes Care*, 2007;30(3):542–8.
6. Hermanns N, Kulzer B, Krichbaum M, et al., *Diabetologia*, 2006;49(3):469–77.
7. Gold EA, MacLeod KM, Deary IJ, Frier BM, *Physiol Behavior*, 1995;58:501–11.
8. Hermanns N, Kubiak T, Kulzer B, Haak T, *Biol Psychol*, 2003;63(1):15–44.
9. Hermanns N, Scheff C, Kulzer B, et al., *Diabetologia*, 2007;50(5):930–33.
10. Goldney RD, Phillips PJ, Fisher LJ, et al., *Diabetes Care*, 2004;27(5):1066-–70.
11. Moussavi S, Chatterji S, Verdes E, et al., *Lancet*, 2007;370(9590):851–8.
12. Ciechanowski PS, Katon WJ, Russo JE, *Arch Intern Med*, 2000;160(21):3278–85.
13. Katon WJ, Von Korff M, Lin EH, et al., *Arch Gen Psychiatry*, 2004;61(10):1042–9.
14. Gonzales JS, Peyrot M, McCarl LA, et al., *Diabetes Care*, 2008;31(12):2398–2403.
15. Lustman PJ, de Groot M, Anderson RJ, et al., *Diabetes Care*, 2000;23:934–42.
16. Black SA, Markides KS, Ray LA, *Diabetes Care*, 2003;26(10): 2822–8.
17. Egede LE, Nietert PJ, Zheng D, *Diabetes Care*, 2005;28(6):1339–45.
18. Zhang X, Norris SL, Gregg EW, et al., *Am J Epidemiolo*, 2005;161(7):652–60.
19. Katon WJ, Rutter C, Simon G, et al., *Diabetes Care*, 2005;28(11):2668–72.
20. Egede LE, Zheng D, et al., *Diabetes Care*, 2002;25(3): 464–70.
21. Egede LE, *Diabetes Care*, 2004;27(7):1751–3.
22. Egede LE, Diabetes, *Diabetes Care*, 2004;27(2):421–8.
23. Peyrot M, Rubin RR, *Diabetes Care*, 1999;22(3):448–52.
24. Hermanns N, Kulzer B, et al., *Diabetes*, 53(Suppl. 2):A16.
25. Lustman PJ, Griffith LS, Clouse RE, et al., *Psychosomatic Medicine*, 1997;59(3):241–50.
26. Lustman PJ, Griffith LS, Freedland KE, et al., *Ann Intern Med*, 1998;129(8):613–21.
27. Lustman PJ, Freedland KE, Griffith LS, *Diabetes Care*, 2000;23(5):618–23.
28. Lustman PJ, Clouse RE, Nix BD, et al., *Arch Gen Psychiatry*, 2006;63(5):521–9.
29. Paile-Hyvarinen M, et al., *BMC Fam Pract*, 2007;8(1):34.
30. NIH, 4. Guideline: Depression co-orccuring with other general medical disorders, 1993.
31. Rubin RR, Ciechanowski P, Egede LE, et al., *Current Diabetes Reports*, 2004;4(2):119–25.
32. Pouwer F, Beekman AT, Lubach C, Snoek FJ, *Patient Educ Couns*, 2006;60(2):235–40.
33. ADA, *Diabetes Care*, 2007;30(Suppl. 1):S4–41.
34. Petrak F, Herpertz S, Kulzer B, Rose M, Results of the German Multicenter Diabetes Cohort Study (GMDC-Study), 2005.
35. IDF Clinical Guidelines Task Force, Global guidelines for type 2 diabetes. Brussels: International Diabetes Federation, 2005.
36. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, *Can J Diabetes*, 2003;27(Suppl. 2):1–152.
37. National Screening Committee, The UK´s National Screening Committee´s criteria for appaising the viability, effectiveness and appropriateness of a screening programme, 2007. Available at: www.nsc.nhs.uk/pdfs/criteria.pdf
38. Peyrot M, Rubin RR, *Diabetes Care*, 1997;20(4):585–90.
39. Hermanns N, Kulzer B, Krichbaum M, et al., *Diabet Med*, 2005;22(3):293–300.
40. Arroll B, Khin N, Kerse N, *BMJ*, 2003;327(7424):1144–6.
41. Lustman PJ, Clouse RE, Griffith LS, et al., *Psychosomatic Medicine*, 1997;59(1):24–31.
42. Awata S, Bech P, Yoshida S, et al., *Psychiatry Clin Neurosci*, 2007;61(1):112–19.
43. Gilbody S, Bower P, et al., *Br J Psychiatry*, 2006;189:297–308.
44. Gilbody S, Sheldon T, et al., *BMJ*, 2006;332(7548):1027–30.
45. Gilbody S, House AO, Sheldon TA, *Cochrane Database of Systematic Reviews*, 2005;(4):CD002792.
46. Simon GE, Katon WJ, Lin EH, et al., *Arch Gen Psychiatry*, 2007;64(1):65–72.