Endotext

DIABETES AND DEPRESSION

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ABSTRACT

Depression is characterized by a disturbance of mood, affecting between 3–5% of the general population at any one time. The prevalence of depression is approximately doubled in people with diabetes compared to the general population, with similar rates between type 1 diabetes and type 2 diabetes. Although many cases of depression are coincidental to the presence of diabetes, certain diabetes factors including diabetes-related complications, diabetes treatments and obesity are associated with an increased risk of depression. There is a bi-directional relationship between diabetes and depression with specific disease and treatment factors explaining why diabetes pre-disposes to depression and vice versa. Genetics, early intra-uterine development, and social determinants of health may create a “common soil” for both conditions. The presence of depression in people with diabetes worsens both diabetes and depression outcomes. Mortality is increased, quality of life diminished, and healthcare costs are increased. Diabetes self-management is also impaired. It may be possible to reduce the incidence of depression in people with diabetes by considering the way in which the diagnosis of diabetes is conveyed and the psychosocial support that is given through an individual’s journey with diabetes. Several short screening questionnaires have been validated in people with diabetes. A diagnosis should be confirmed by a diagnostic interview. The main aims of treatment are to improve both diabetes and mental health outcomes with complete remission of depressive symptoms. Various psychological treatments, including cognitive behavioral therapy, problem-solving, and psychodynamic techniques have been used to treat depression in people with diabetes. Antidepressants reduce depressive symptoms in people with diabetes as well as the general population. All antidepressants appear to have similar effects on depressive symptoms as long as adequate doses are used. Treatment should be maintained for at least 4–6 months after remission of symptoms to reduce the risk of relapse and recurrence. The choice of antidepressant depends largely on the side-effect profile, individual preference, and response. Selective serotonin reuptake inhibitors are widely used as first-choice agents. A common model of care for depression is the Stepped Care Model which is designed to provide a rational approach to the treatment of depression, while reducing costs and side effects of antidepressants through more appropriate prescribing. A case management model known as *collaborative care* is a clinical- and cost-effective treatment of depression that also improves diabetes outcomes by involving a multidisciplinary team that works together to identify and treat depression within primary care settings. Although diabetes and depression remain a considerable clinical challenge, there are grounds for considerable optimism as the scientific knowledge that underpins clinical practices has expanded markedly in the last two decades. However, further research is needed to understand what can be done to prevent depression in people with

diabetes and to identify the optimal treatment for an individual that improves both depressive symptoms and diabetes outcomes.

INTRODUCTION

The importance of considering the interaction between mind and body in the management and outcome of chronic diseases has been recognized for over 2,500 years but is particularly poignant for people with diabetes. Diabetes places high behavioral demands on those living with the condition whilst mental disorders, such as depression, may compromise an individual's ability to perform the self-care needed to optimize health and prevent the long-term consequences of diabetes. Much of diabetes care is focused around the identification and treatment of long-term diabetes-related complications and diabetes healthcare professionals are adept in managing microvascular and macrovascular conditions. An appreciation, however, of the psychological consequences of diabetes has lagged behind, despite these being common and the morbidity, mortality, and health costs associated with the co-morbidity being disproportionately increased compared with the effects of either condition alone (1, 2).

Several factors contribute to the poorer health outcomes seen in people with diabetes and mental disorders. Despite the increased burden of disease, people with co-morbid mental disorders have often been disadvantaged by health services and have received sub-optimal medical care (3). They have been less likely to receive the necessary diabetes processes of care, self-management education, and cardiovascular preventative medication despite increased visits to their primary healthcare teams and despite similar interest in caring for their physical illness as the general population (4). Clinicians may fail to recognize that those with mental illness are more likely to develop physical illnesses and so physical complaints are either ignored or not taken seriously. Mental health symptoms often "over-shadow" other complaints leading healthcare professionals to focus on the mental illness to the detriment of any physical illness (5). Health services are often poorly configured with clinics focusing on either the treatment of physical illnesses or mental disorders rather than treating both conditions at the same time (3). The stigma associated with mental illness may prevent people and their families from seeking help for mental illness, thereby depriving them of effective treatments, which not only harms mental well-being but is detrimental to diabetes management (6).

Diabetes and mental disorders are both common, and so a degree of co-occurrence would be expected purely by chance. The evidence suggests, however, that diabetes is more frequently associated with a range of mental and psychosocial disorders than expected (7, 8). Furthermore, several mental disorders, including depression, are associated with an increased risk of developing diabetes. An understanding of this complex interaction is crucial to the management and outcome of people with diabetes.

This chapter focuses on the co-morbidity of diabetes and depression; both are common, are relatively easy to diagnose, and have established effective treatments (8). They may also serve as an exemplar for other mental disorders and provide a model for the successful management of other co-morbid mental and physical health conditions. The chapter will describe the epidemiology of diabetes and depression and will discuss the mechanisms underlying the association between diabetes and depression. It will also highlight the clinical implications and consequences of co-occurring diabetes and depression. Diabetes healthcare professionals need to be aware of how to screen for depression and to provide "first response" management, while recognizing when to refer for specialist psychiatric care (9).

DEPRESSION

Depression belongs to a group of mental disorders where the primary abnormality is a disturbance of mood. The cardinal features of depression are low mood, and loss of interest or pleasure, lasting longer than two weeks. During a depressive episode, other symptoms may include poor concentration, feelings of excessive guilt or low self-worth, hopelessness about the future, thoughts about dying or suicide, disrupted sleep, changes in appetite or weight, and feeling especially tired or low in energy. People with depression are at an increased risk of suicide. Depressive symptoms exist on a continuum of severity, and it is important to recognize that depression is different from usual fluctuations in mood that occur with everyday life.

Major depressive disorder (also known as clinical depression, unipolar depression, or major depression) is defined by the diagnostic criteria of the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5), based on the number and duration of symptoms (Table 1) (10). The DSM-5 definition approximates a level of severity of symptoms that is associated with both disability and dysfunction. DSM-5 also recognizes several sub-types of depressive disorder where the symptoms are less severe but nevertheless may still compromise diabetes self-care and outcomes.

Table 1. DSM-5 "Major" Depressive Episode
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. • Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful). • Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others). • Significant weight loss when not dieting or weight gain (e.g. a change of >5% of body weight in a month) or decrease or increase in appetite nearly every day. • Insomnia or hypersomnia nearly every day. • Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). • Fatigue or loss of energy nearly every day. • Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). • Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). • Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The symptoms are not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition (e.g. hypothyroidism).

Epidemiology of Depression

Depression is one of the commonest mental disorders, affecting between 3–5% of the general population at any one time; the lifetime prevalence is 8-12% but there is considerable geographical variation ranging from 3% in Japan to 17% in India. The highest rates of depression are found in the United States of America (USA), the Middle East and South Asia (11). In 2019, 280 million people were living with depression, including 23 million children and adolescents (12). The incidence of depression worldwide increased by 50% between 1990 and 2017 to an age standardized rate of 3.25 per 1000 (13). Depressive disorders are now ranked as the single largest contributor to non-fatal health loss (7.5% of all years lost to disability) (14).

Depression can affect any age group, with depression being seen in infants as young as 6 months old after separation from their mothers (15). The commonest age of onset is between the ages of 30 and 40 years, but there is a second, smaller peak in incidence between ages 50 and 60 years (16). The risk of depression is doubled in women compared with men (17). Although the cause of depression remains uncertain, other risk factors for a depressive episode are recognized and include a family history of depression, certain personality types, childhood adversity, the postpartum period, social isolation, and a lack of close interpersonal relationships (18). An episode of depression is often triggered by a stressful life event, particularly for the first few depressive episodes (Table 2). Depression may accompany other mental illnesses and long-term physical conditions (19). All these risk factors apply to people living with diabetes and so consequently much of the depression seen in people living with diabetes is coincidental to the diabetes.

Table 2. Risk Factors for Depression

- Female gender
- Age
- Family History
  - Genetics
  - Shared Environment
- Personality type
  - Introversion
  - Neuroticism
    - Insecure, worried
    - Obsessive
  - Unassertive, dependent
  - Low conscientiousness
  - Disorganization
  - Stress-sensitive
- Childhood adversity
  - Separation
  - Neglect
  - Abuse
    - Mental
    - Physical
    - Sexual
  - Early bereavement
  - Unequal parental treatment of siblings
- Mental illness
  - Schizophrenia
  - Drug or alcohol misuse
- Physical illness
  - Infection
    - HIV
  - Nutritional deficiencies
  - Cardiovascular disease
    - Myocardial infarction
    - Stroke
  - Pernicious anemia
  - Neurological
    - Parkinsonism
    - Multiple sclerosis
  - Endocrine
    - Diabetes
    - Obesity
    - Hypoandrogenism
    - Cushing syndrome
    - Hypothyroidism
    - Hyperparathyroidism
  - Cancer
  - Arthritis
  - Chronic pain

• Life Events
  ○ Childbirth
  ○ Menopause
  ○ Rape or assault
  ○ Natural disasters
  ○ Job loss or unemployment
  ○ Stress
  ○ Financial difficulties
  ○ Bullying
  ○ Relationship or marriage breakdown
  ○ Bereavement
  ○ Catastrophic injury
	○ Inflammation
	• Side effects of medication
	  ○ β-blockers
	  ○ α-interferon
	  ○ Finasteride
	  ○ Isotretinoin
	  ○ Dopamine receptor agonists
	  ○ Some anticonvulsants
	  ○ Some antimigraine agents
	  ○ Some antipsychotics

DIABETES AND DEPRESSION

The association between diabetes and depression has been recognized for many years. In the 17th century, Thomas Willis, an English physician, described how "*diabetes is a consequence of prolonged sorrow"* (20). Until the last two decades, the focus of any discussion of mood and diabetes was on the increased likelihood of depression in people with diabetes, where the comorbidity was viewed as an *understandable* reaction to the difficulties and challenges of living with a demanding and life-limiting long-term physical illness. In this regard, it was treated no differently from other long-term physical conditions that are also associated with increased rates of depression. We now understand that the relationship between the two conditions is more complex and, at least for type 2 diabetes, is bidirectional (8).

Understanding the scale of the co-morbidity is challenging because the epidemiological studies examining the relationship have been hampered by considerable variation in measurement, study design, and use of terminology that have contributed to significant heterogeneity and inconsistency between studies (8). An example of this variability is illustrated by one meta-analysis that reported a range of prevalence rates of depression in people with diabetes from 1.8% to 88% (21).

The *gold standard* for the diagnosis of depression is a diagnostic interview, but many studies have relied on self-rating scales (22). These scales identify *depressive symptoms* rather than *depression* and do not differentiate between symptoms that could be caused by either diabetes or depression, for example, fatigue or weight change. This can lead to significant overestimates of the prevalence of *depression* in those with diabetes, as shown in an early meta-analysis where the prevalence of depression in people with diabetes identified by diagnostic interview was 11.4% compared to 31.0% in studies using self-rating questionnaire (23). However, a more recent meta-analysis argued that the symptom overlap does not affect prevalence (21). Nevertheless, the authors argue that depression measures that focus on the cardinal symptoms of depression rather than overlapping symptoms may most accurately diagnose depression.

Studies have often used mixed populations of people with type 1 diabetes and type 2 diabetes. This distinction is important because people with type 2 diabetes are generally older, and depression prevalence varies with age (16). There are differences in the prevalence of diabetes-related complications and other comorbid conditions such as obesity and heart disease, which independently affect the likelihood of developing depression (24). The pathogenesis and etiology of the two main types of diabetes differ, which may affect the risk of depression

in different ways (25). Finally, the burden of management differs between type 1 diabetes and type 2 diabetes.

Many studies have not taken broad population approaches but have concentrated on *convenience* samples, usually drawn from specialist diabetes clinics, where the participants may not reflect the wider population of people living with diabetes. This bias is illustrated in the meta-analysis by Farooqi et al which reported that the prevalence of depression in people with diabetes was 36% in studies carried out in specialist care compared to 12% in community or primary care settings (26). Biases may also occur where there are low or unknown response rates, because the presence of depressive symptoms may affect the willingness of an individual to participate.

A further confounding factor is the concept of *diabetes distress* which describes the emotional response to living with diabetes, including the demands of self-management, the threat of complications, the social impact of stigma and discrimination, and the financial costs of treatment (27). Diabetes distress can fluctuate over time and may peak during challenging periods such as soon after diagnosis, during major treatment changes, or during the development or worsening of long-term complications (Table 3). Diabetes distress is distinct from depression in its association with self-management and glycemic levels, but the two conditions may co-exist in about 5-15% of people with diabetes. By contrast depression occurs without distress in 5-10% of people while distress alone affects 20-30% (28). The importance of diabetes distress was first proposed in 1995, and it is likely that early studies of diabetes and depression were capturing distress as well as depression, thereby contributing to an overestimate of the prevalence of depression.

Table 3. Common Features of Diabetes Distress

- Feeling overwhelmed by the demands of living with diabetes
- Feeling concerned about “failures” with diabetes management
- Feeling powerless or hopeless
- Worrying over the risk of low blood glucose or long-term complications
- Feeling frustrated that diabetes cannot be predicted or controlled from one day to the next
- Feeling frustrated with care givers
- Feeling guilty when the diabetes management go ‘off track’.

Despite these caveats, several meta-analyses have indicated that the prevalence of depression is approximately doubled in people with diabetes compared to the background population (23, 26), with the prevalence of depression similar between type 1 diabetes (22%) and type 2 diabetes (19%) (26). Although most studies come from Western Europe or North America, the increased rates of depression or depressive symptoms have been found across the world (29, 30), with the prevalence being higher in low- and middle-income countries (26). A meta-analysis of 248 observational studies including over 8 million people with type 2 diabetes found a global prevalence of depression of 28%, with the highest rates observed in Asia and Australia whilst the lowest rates were found in studies from Europe (31). Cohort studies have shown an increase in incident depression in people with diabetes; one meta-analysis of 11 studies involving approximately 50,000 people with type 2 diabetes but without depression at baseline reported that the incidence of depression was 24% higher in people with diabetes (32), while another meta-analysis of 13 studies found incident depression was increased by 15% in people with diabetes (33).

An increased prevalence of depression has also been found in children with diabetes. A meta-analysis of 109 studies involving over 50,000 children with diabetes

estimated that the prevalence of depression was 22.2% among children with type 1 diabetes and 22.7% in children with type 2 diabetes (34). Consistent with studies in adults, the prevalence of depression was higher among girls than boys (29.7% vs. 19.7%) and in low- to- middle-income countries.

Type 2 diabetes is a common comorbidity in people with mental disorders, with a reported prevalence ranging from 5% to 22% depending on the specific psychiatric disorder. Overall, the prevalence of diabetes in people with depression is 9% but there is considerable heterogeneity between studies (35). Consistent with this finding, the incidence of diabetes in people with depression is increased by 18-60% (33, 36, 37). People with depression, however, may receive more screening for diabetes than those without because of their increased contact with healthcare professionals and an awareness of the risk of diabetes by mental health practitioners, which may lead to an overestimate of the difference in diabetes risk between those with and without depression, particularly in studies that rely on routinely collected healthcare data.

Diabetes Factors That Increase the Risk of Depression

Although many cases of depression are coincidental to the presence of diabetes, certain diabetes factors including diabetes-related complications and obesity are associated with an increased risk of depression (38).

DIABETES COMPLICATIONS

The development of macrovascular and microvascular complications increases the risk of depression in people with type 1 diabetes and type 2 diabetes (24, 39). Overall, the presence of diabetes complications increases the risk of incident depressive disorder by 14% but the increased risk of developing depression is 24% higher for microvascular complications compared with 9% higher for those with macrovascular complications (39). The risk of depression increases as more complications develop such that the presence of two or more complications more than doubled the risk of depression in people with type 2 diabetes in one specialized outpatient clinic, with neuropathy and nephropathy showing the strongest association (40).

DIABETES TREATMENTS

The use of insulin in type 2 diabetes is associated with higher rates of depression compared to non-insulin medications or dietary and lifestyle interventions alone. One meta-analysis of 28 studies reported an overall 59% higher risk of developing depression in people taking insulin and 42% higher risk when compared with oral anti-diabetes agents (41). It seems unlikely that insulin *per se* increases depressive symptoms, but insulin is associated with higher treatment demands that not only include self-injection but more intensive self-monitoring, which may adversely affect depressive symptoms (42). Insulin is also used in those with longer duration of type 2 diabetes, which may be associated with a higher prevalence of diabetes-related complications and elevated HbA_{1c}, a further risk factor of depression (43). Insulin has been used erroneously as a threat by healthcare professionals to encourage people to follow certain health behaviors or take medications. As type 2 diabetes is associated with progressive β-cell decline, many people ultimately need insulin. Where insulin has been used as a threat, commencing insulin can evoke feelings of guilt, blame or failure, which may increase the likelihood of depression. Furthermore, people may have strongly held beliefs about insulin usage, seeing it as an “end of the road” treatment. They may also associate insulin with the development of diabetes complications or death if they have seen a family member with diabetes developing complications while using insulin. Insulin therapy is associated with significant weight gain, again a risk factor for depression, and an increased risk of hypoglycemia. In a 10-year study of 3,742 people with type 1 diabetes requiring emergency room visit or

hospitalization, those admitted with a hypoglycemic event were 74% more likely to develop depression (43).

Other anti-diabetes treatments, by contrast, may be associated with a reduced risk of depression and there has been discussion about whether these could be re-purposed as treatments for depression (44). A meta-analysis of current therapies indicated that pioglitazone was associated with improved depressive symptoms, more so in women, but metformin had no consistent benefit (44). A more recent systematic review, however, suggested that metformin might help treat comorbid depression, although the evidence was too weak to recommend its use for this indication (45). A review of observational studies also indicated that metformin was associated with reduced depressive symptoms (46). GLP-1 receptors are widely expressed in the brain and have putative neuroprotective properties. A meta-analysis of six studies including 2,071 participants showed a small but significant reduction in depressive symptoms in those treated with GLP-1 receptor agonists (47). Whether the improvement is a direct effect or mediated through weight loss is unknown. This observation was also seen in a large population-based cohort and nested case-control study that found that low doses of metformin, dipeptidyl peptidase-4 (DPP4) inhibitors, GLP-1 receptor agonists, and sodium-glucose transporter 2 (SGLT2) inhibitors were associated with lower risk of depression in people with diabetes compared to those using other treatments, with the lowest risk seen with SGLT2 inhibitors (48). Further studies of the impact of SGLT2 inhibitors are warranted as abnormal brain bioenergetic metabolism occurs in depression and endogenous ketones may exert a neuroprotective effect that might improve mood. As SGLT2 inhibitors induce ketogenesis, there is a rationale to test whether SGLT2 inhibitors improve depressive symptoms (49).

MECHANISMS TO EXPLAIN THE LINK BETWEEN DIABETES AND DEPRESSION

No one mechanism explains the association between diabetes and depression, but specific disease and treatment factors may account for why diabetes predisposes to depression and vice versa (Figure 1). These are, however, superimposed on other factors, such as genetics, early intra-uterine development, and social determinants of health, that create a “common soil” for both conditions.

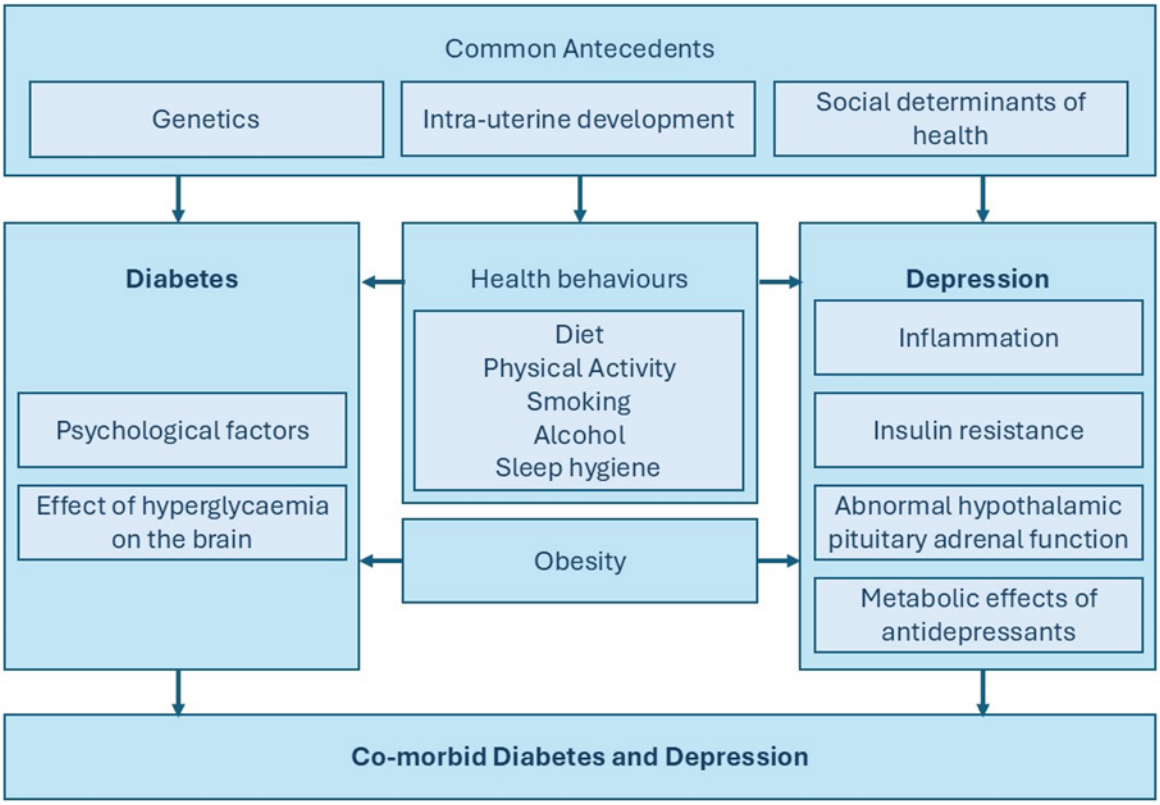

Figure 1. The possible mechanisms that lead to the co-morbidity of diabetes and depression.

Underlying Factors That Predispose to Both Diabetes and Depression

GENETICS

Modern genetic technologies, such as genome-wide association (GWAS) studies and Mendelian randomization analyses have revolutionized our understanding of how genetics may underlie many polygenic mental and physical disorders and their association as well as health behavior traits, such as smoking and alcohol consumption that influence health. These studies have shown overlap of genetic polymorphisms that increase the risk of several mental disorders, including depression, and physical disorders, including diabetes, metabolic syndrome, and obesity (50). There are nearly 500 single nuclear polymorphisms that are associated with an increased risk of both diabetes and depression across a broad range of pathways that include immune function, lipid metabolism, cancer-related pathways, and cell signaling (51).

FETAL DEVELOPMENT

The 'developmental origins of health and disease' hypothesis emerged from epidemiological studies that found that infants with low birth weight had an increased risk of cardiovascular disease, diabetes, and other chronic conditions in adulthood (52, 53). Although the early studies focused on physical illness, the fetal environment is linked to psychiatric conditions, including depression, although the effect size is weak and inconsistent across studies (54).

SOCIAL DETERMINANTS OF HEALTH

The broad conditions in which people are born, live, learn, work, play, worship, and age affect a wide range of health, functioning, and quality-of-life outcomes and risks throughout the life course, which together are

known as the 'social determinants of health' (55). These can be divided into macro-level factors, such as government policy, meso-level factors, such as neighborhood and workplace, and individual factors, such as health behaviors and are broadly grouped into five domains: economic stability, educational access and quality, health care access and quality, neighborhood and built environment, and social and community context, which include gender and race. These social factors are more robust predictors of population health than either the provision of healthcare services or individual health behaviors and explain up to 80% of a person's health (56).

Many of the risk factors for depression described earlier in the chapter include or are affected by social factors, such as childhood adversity, low socio-economic status, or lived environment. Many of these same factors also affect the risk of diabetes. For example, access to recreational spaces, safe housing and surroundings, clean air, and shops that sell nutritious and wholesome foods provide an environment where an individual can more easily choose behaviors that would reduce the risk of diabetes.

Diabetes-Specific Factors

Both psychological and biological mechanisms contribute to the increased risk of depression in people with diabetes.

PSYCHOLOGIOCAL FACTORS

The psychological model proposes that depression is an understandable response to the difficulties of living with a demanding and life-shortening long-term physical illness that is associated with potentially debilitating complications. This model is supported by a systematic review of 11 studies that found no difference in the prevalence of depression between those with undiagnosed diabetes, those with impaired glucose metabolism, and people with normal glucose metabolism (57). By contrast, an increased prevalence of depression was only found in those with diagnosed diabetes suggesting that the *knowledge* of the diagnosis and the burden of managing the condition and its complications are associated with the development of depression. A more recent meta-analysis showed an 11% and 27% increased risk of depression in those with pre-diabetes and undiagnosed diabetes, respectively, compared with people with normal glucose metabolism but this was lower than the 80% increase in those with known diabetes (58). The increase was only seen in people aged less than 60 years old and was partially explained by the presence of comorbid cardiovascular disease. Since this publication, studies from Mexico (59), Germany (60) and rural China (61) did not find increased rates of depression in people with undiagnosed diabetes. However, a large study from the Netherlands found a similarly increased rate of depression in those with diagnosed and undiagnosed diabetes (62).

Although these findings generally support the psychological model, it is important to recognize that the people with undiagnosed diabetes differ from those with diagnosed diabetes by more than just the knowledge of their condition. For example, those with diagnosed diabetes are likely to have had diabetes for longer and have developed complications and other co-morbidities that may affect their risk of depression.

EFFECT OF DIABETES ON BRAIN STRUCTURE AND FUNCTION

It is well recognized that acute hyperglycemia and hypoglycemia can affect mood (63, 64). This is unsurprising because the brain is dependent on a continuous supply of glucose as its principal source of energy, and changes in blood glucose levels rapidly affect cerebral function. However, longer term effects of diabetes on brain structure and function have also been seen in animal models of diabetes and in humans. In animals, diabetes negatively affects hippocampal integrity and neurogenesis, both of which are areas that are important in cognition and mood

(65). In adults with type 1 diabetes, magnetic resonance imaging (MRI) studies have shown hippocampal atrophy together with increased prefrontal glutamate-glutamine-gamma-aminobutyric acid (GABA) levels in a way that correlates with mild depressive symptoms (65, 66). In the brain, insulin stimulates glucose uptake, in part by increasing the synthesis of the glucose transporters in neurons and neuroglia (67). Consequently, abnormal insulin signaling in the brain could affect glucose transport across the blood-brain barrier leading to reduced neuronal glucose uptake and neuronal loss. As the amygdala and hippocampus are the regions that contain a high density of insulin receptors, they may be disproportionately affected by insulin resistance, which is independently associated with depression (68).

At a cellular level within the hippocampus, diabetes is associated with an increase in astrocytes and microglia reactivity and apoptosis of pyramidal neurons, and reduced neurogenesis and synaptic plasticity with dendritic retraction (69). In addition to the changes in GABA, there are other molecular changes, including increased glucocorticoid signaling, reduced brain-derived neurotrophic factor (BDNF) production, increased mGluR2/3 activity and caspase 3 activation, and an increase in the TLR4/NFκB signaling pathway, together with increased production of reactive oxygen species and pro-inflammatory cytokines, such as TNF-β. These changes lead to increased apoptosis and decreased progenitor proliferation, which in turn lead to a decrease in the hippocampal size.

Depression-Specific Factors

Depression may increase the risk of diabetes through health behaviors as well as the biological effects of depression and its treatment with antidepressants.

ADULT HEALTH BEHAVIORS

Health behaviors play an important role in determining an individual's risk of developing diabetes.

Diet

A healthy diet protects against many long-term conditions including diabetes, obesity, and depression. Both epidemiological studies and intervention studies have shown how maintaining normal weight, reducing fat, particularly saturated fat, and increasing the fiber content of the diet reduces the risk of type 2 diabetes (70, 71). Certain dietary patterns, such as the Mediterranean diet, are associated with a lower risk of diabetes (72).

High levels of refined sugars and saturated fats may also increase the risk of depression, while a Mediterranean diet and diets that include more vegetables, fruits, fish, and whole grains seem to be protective (73). Once present, depression may entrench less prudent eating habits, creating a vicious cycle where poor diet and depression reinforce each other while simultaneously increasing the risk of diabetes. Depression increases the risk of obesity, with those with depression being 58% more likely to develop obesity than those without (74).

Excessive alcohol intake is associated with an increased risk of diabetes (75). Alcohol misuse is one of the most prevalent mental disorders, especially in more affluent countries (76). About a quarter of those with alcohol dependency have co-morbid mental disorders including depression, where alcohol is often used as a coping mechanism to manage stress, anxiety, or depressive symptoms.

Physical Activity

The health benefits of physical activity are overwhelming and include a lowered risk of type 2 diabetes and depression. There is a graded response with some physical activity being better than none, but further benefits accrue with more physical activity. Avoidance of sedentary behavior is also important for health. People with depression are less physically active than the general population; a meta-analysis of 24 studies including 2901 people with major

depression disorder found that compared to the general population, those with depression spent less time engaged in overall and moderate to vigorous physical activity and were more likely to be sedentary. People with depression were 50% less likely to meet the recommended physical activity guidelines of taking at least 150 minutes of moderate-to-high intensity physical activity in a week through a variety of activities (77). Over two-thirds of people with depression do not reach this target (78).

Smoking

Tobacco use is the single most preventable cause of death and disease throughout the life-course and increases the risk of diabetes by 30-40% (79, 80). Smoking is one of the most important modifiable risk factors of physical morbidity and mortality in people with mental illness (81). Adults with depression are twice as likely to smoke as adults without depression. There also appears to be a bi-directional relationship where smoking increases the risk of depression while people with depression are more likely to start smoking (82).

Sleep

The health benefits of sleep include a lower risk of diabetes and maintenance of a healthy weight (83). Sleep problems are a cardinal feature of depression with difficulty falling asleep and waking during the night, being common symptoms of depression (10).

BIOLOGICAL EFFECTS OF DEPRESSION

Several biological changes occur during an episode of depression that might increase the risk of diabetes. First, acute episodes of depression are associated with hyperinsulinemia and insulin resistance and are unaffected by antidepressant treatment (68). Depression is also associated with a state of chronic inflammation that is characterized by increased C-reactive protein, TNF-α, and proinflammatory cytokines that might partially explain the change in insulin sensitivity. These proteins are linked to sickness behavior in animal models of depression and in humans are associated with an increase in type 2 diabetes and the metabolic syndrome (84, 85). Depression is further associated with abnormalities of hypothalamic-pituitary adrenal (HPA) axis function, which manifests as subclinical hypercortisolism, blunted diurnal cortisol rhythm, or hypocortisolism with impaired glucocorticoid sensitivity (86). Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor expressed in several tissues, including the brain, gut, and pancreas. As described earlier, BDNF plays an important role in maintaining neuronal plasticity, including neurogenesis, synaptogenesis, and neuronal maturation. Depression decreases BDNF expression in the hippocampus and prefrontal cortex (87). Outside the brain, BDNF activation leads to reduced hepatic gluconeogenesis, increased hepatic insulin signal transduction, and protects against pancreatic β-cell loss. Serum BDNF concentrations are lower in people with diabetes (88).

ANTIDEPRESSANTS

Although essential components of the management of depression, it is possible that the use of antidepressants contribute to the risk of diabetes. Case reports, and observational studies have generally shown that people receiving antidepressant medications have a higher risk of diabetes but whether this relationship is causative remains unproven (89, 90). Randomized controlled trials have emphasized that antidepressants vary considerably in their association with weight gain and both hyperglycemia and hypoglycemic effects have been observed (89). Some antidepressants, including paroxetine, mirtazapine, and various tricyclic antidepressants are associated with significant weight gain which could increase the risk of diabetes in the long term. By contrast, buproprion is associated with weight loss (91).

CONSEQUENCES OF DIABETES AND DEPRESSION CO-MORBIDITY

The presence of depression in people with diabetes worsens both diabetes and depression outcomes (Figure 2).

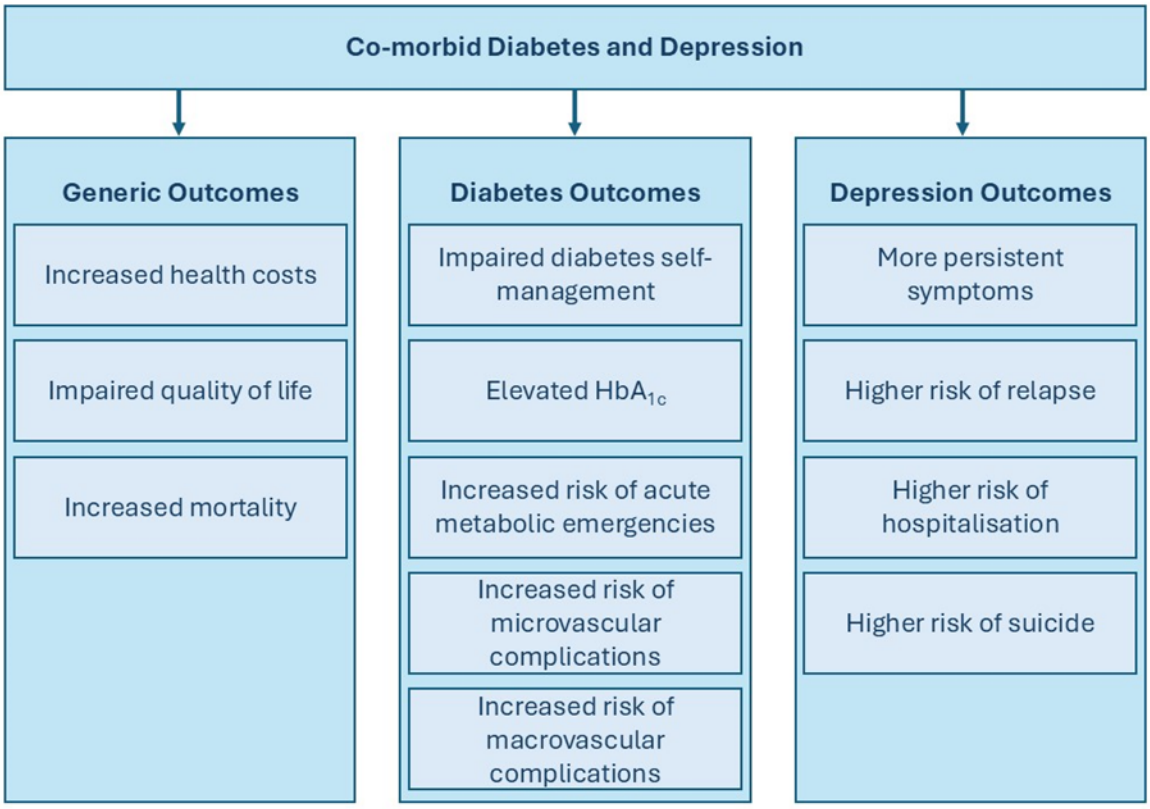

Figure 2. The consequences of living with diabetes and depression.

Mortality

Mortality rates from physical illnesses, including cardiovascular disease, cancer, and diabetes, are higher in people with depression. Among people with diabetes, depression increases the risk of mortality by approximately 50% (92, 93). Where depression co-exists with anxiety, which is also more common in people with diabetes, mortality rates are further increased (94).

Depression Outcomes

Once depressive symptoms occur or a diagnosis of depression is made, the symptoms appear to be persistent and likely to recur in people with diabetes. A longitudinal study of 2,460 people with type 2 diabetes in a primary care setting found that 26% met the criterion for depression on at least one occasion, with incident depression occurring in 14% over a 3-year period (95). Recurrent or persistent depression occurred in two-thirds of those with baseline depression. In two other studies from the USA, self-reported depressive symptoms persisted in 73% of people 12 months after a diabetes education program (96) while major depressive disorder relapsed in 79% of people with diabetes over a 5-year period (97).

Depression is a major cause of excess hospitalization in people with diabetes and is the leading cause of psychiatric admissions in people with diabetes accounting for 6.1 admissions per 1,000 person years

in people with type 1 diabetes and 7.05 admissions in people with type 2 diabetes in Australia, with higher admission rates for women (98). These rates are 2-3-fold higher than the general Australian population (99).

People with diabetes have an increased risk of completed suicide compared with the general population and are more likely to report suicidal ideation, one of the strongest predictors of completed suicide, and intentional self-harm (100). The risk of suicidal behavior is highest in young people with type 1 diabetes, in whom suicide may account for up to 7% of deaths. Suicidal ideation is also increased among adolescents and young adults with type 1 diabetes compared with the general population (15.0% vs. 9.4%) and is seen in all ethnic groups (101). It is likely, however, that the true incidence of suicidal attempts and completed suicides is considerably higher amongst people with diabetes because of ineffective identification and coding (100). Many hospital admissions for diabetes ketoacidosis or hypoglycemia of 'unknown' etiology result from insulin omission or overdose, but whether these are deliberate acts is frequently unrecognized or unrecorded. There is also anecdotal evidence that healthcare professionals are unwilling to record suicide as a cause of death because of the associated stigma. Suicide rates are higher in people with long-term health conditions than in people in the general population, but what makes diabetes stand out is access to insulin, providing a means for suicide either by omission or overdose, the latter of which is the commonest method of suicide in people with insulin-treated diabetes.

Diabetes Outcomes

ACUTE METABOLIC COMPLICATIONS

People with type 1 diabetes and depression have an increased risk of admission to hospital with diabetic ketoacidosis and severe hypoglycemia. In one study involving 3,742 people with type 1 diabetes who attended the emergency room or who were admitted to hospital between 1996 and 2015, those with depression had a 2.5-fold increased risk of severe hyperglycemia events and an 89% increased risk of severe hypoglycemia (43). The risk was greatest within the first 6 months following a diagnosis of depression, when the risk was 7.14-fold higher for hyperglycemia events and 5.58-fold higher for hypoglycemia.

MICROVASCULAR COMPLICATIONS

An early meta-analysis showed that the risk of microvascular complications was increased with small to moderate weighted effect sizes of 0.17 to 0.32 (24). The increased risk was similar in people with type 1 diabetes and people with type 2 diabetes while sexual dysfunction and painful peripheral neuropathy seemed to be associated with the highest risk. Most of these studies were cross-sectional but a more recent meta-analysis of 16 studies that examined the relationship between baseline depression and incident diabetes complications found that depression was associated with a 33% increased risk of incident microvascular disease (39). Most studies reported a composite of neuropathy, retinopathy, and nephropathy but one study reported nephropathy alone and found a 18% increase in incident chronic kidney disease (102). Depression is associated with a 68% increased risk of a first diabetes-related foot ulcer but not ulcer recurrence (103). This contrasted an earlier study that found a third of all individuals with diabetes-related foot ulcer had depression and that depression was associated with a threefold increased risk of dying (104).

MACROVASCULAR COMPLICATIONS

A recent meta-analysis has reported that incident macrovascular complications were increased by 38% in people with baseline depression (39). Most studies used a composite macrovascular outcome which included atherosclerotic vascular disease, myocardial infarction, and stroke as well as congestive heart failure and stroke. Some studies also included cardiovascular procedures, such as coronary artery

bypass grafting or other revascularization techniques. Only one study reported separate outcomes for stroke (HR 1.22) and coronary heart disease (HR 1.32) (102).

QUALITY OF LIFE

Quality of life has been assessed by several different measures in people with diabetes and depression, including the Diabetes Specific Quality of Life scale and SF-36. These studies consistently show that quality of life is impaired in people with the co-morbidity (105). The effect of diabetes and depression appears to be additive across several domains with the exception of mental health where most of the effect stems from depression (106).

COST OF TREATMENT

The presence of depression among people with diabetes can substantially increase health care costs. An analysis of 147,095 adults living in the US found that depression and diabetes alone increased healthcare expenditure by $2,654 and $2,692, respectively, compared with neither condition but when both conditions occurred together, the cost was increased by $6,037 (107). Based on these figures, the estimated total cost of treating co-morbid diabetes and depression in the US was $77.6 billion per year. A more recent study found that total health costs increased from $11,550 for people with diabetes alone to $16,511 for people with diabetes and depression (108). This was in part driven by higher rates of hospitalization (26.1% vs 17.4%) and emergency room visits (55.3% vs 43.0%). Ironically, the increased cost occurred despite decreased healthcare utilization. In a US study of 22,642 people with diabetes enrolled in the 2019 Behavioral Risk Factor Surveillance System, those with a diagnosis of a depressive disorder were 82% more likely to report not seeing a doctor because of healthcare costs in the previous year (109).

DIABETES MANAGEMENT

Glycemic Levels

It has been hypothesized that changes in glycemic levels may mediate the association between depression and diabetes micro- and macrovascular complications and mortality. However, studies that have investigated this have produced inconsistent findings. An early meta-analysis reported a small to moderate association between depression and elevated HbA_{1c} for type 1 diabetes and type 2 diabetes, but included mainly cross-sectional studies that precluded an inference on temporality (110). A recent meta-analysis investigated the longitudinal association between self-reported depressive symptoms and HbA_{1c}. The six longitudinal studies had a combined sample size of 3,683 participants who were followed for a mean period of 37 months (range six months to five years). There was a small significant association between baseline depressive symptoms and subsequent HbA_{1c} levels (111). A further meta-analysis of 14 studies in children and adolescents with type 1 diabetes reported a correlation between depressive symptoms and HbA_{1c} (112). The timing of the diagnosis of diabetes and depression may also be important. In a study of 11,837 people with type 2 diabetes registered with the UK Biobank followed for a median of 6.9 years, those diagnosed with major depression decades prior to type 2 diabetes had lower HbA_{1c} over time compared to individuals without depression and those diagnosed closer to their diabetes diagnosis date (113). For individuals whose depression was diagnosed after diabetes, the time since the onset of depression also shaped the trajectory of HbA_{1c}, with the adverse effect of a diagnosis of depression on HbA_{1c} being greatest in those whose diagnosis occurred shortly after the onset of diabetes. Furthermore, the variability of HbA_{1c} within any individual was 16% higher in those with post-diabetes depression (113).

Diabetes Self-Management

Optimizing glucose levels is highly dependent on self-care activities that include regular glucose monitoring, taking medication as prescribed, and engaging in health behavior change to improve diet and physical activity. Depression compromises an individual's ability to self-manage their diabetes. A meta-analysis of 47 studies reported that depression significantly reduced the likelihood of engaging in self-management behaviors, including missed medical appointments, less medication taking and glucose monitoring, and less foot care (114, 115). Similar to anti-diabetes medications, people with co-morbid depression are also less likely to take anti-hypertensive medications and lipid-lowering therapy (115). Depression is associated with a less nutritious diet that is characterized by lower consumption of fruit and vegetables and increased refined carbohydrates (116). Physical activity is reduced while smoking and alcohol consumption is increased (115). The effect of depression appears to be mediated through its adverse effects on self-efficacy and illness perception (115).

MANAGEMENT OF DIABETES AND DEPRESSION

Preventing Depression in People with Diabetes

The implication of the psychological model of depression in diabetes is that healthcare professionals could play an important role in moderating the psychological burden associated with diabetes by considering the way in which the diagnosis of diabetes is conveyed and the psychosocial support that is given through an individual's journey with diabetes. Many people with diabetes experience stigma, some of which stem from their healthcare team. They report feelings of shame and blame because they are held responsible for developing overweight, obesity, or diabetes (117). However well-intentioned the healthcare professional is, it is clear that evoking these feelings is associated with worse clinical outcomes. By contrast, the use of person-centered, non-stigmatizing language can create a trusted and safe space for meaningful clinical discussion (118).

Several individual and group-based interventions with the aim of preventing the development of depressive symptoms have been trialed in people with diabetes. Of the twelve studies reported in a recent narrative review, half had a positive effect (119). Features associated with a reduction in the likelihood of developing depressive symptoms included diabetes self-management education and support, problem-solving and resilience-focused approaches,
and emotion-targeted techniques.

Screening and Diagnosis of Depression

Given the importance of depression in people with diabetes and the availability of effective treatment, there is a strong rationale to screen for depression in people with diabetes (120), not least because depression is under-recognized in clinical practice. Primary care doctors do not diagnose and treat depression in 50–77% of cases (121, 122), while diabetologists only initiate antidepressant treatment in approximately one-third of their patients with clinical depression (123). Similarly diabetes nurses do not recognize depression and anxiety, missing 75-80% of those with the conditions (124).

A formal diagnosis of depression requires a validated interview method, such as the Mini International Neuropsychiatric Interview (MINI) or Composite International Diagnostic Interview (CIDI). No laboratory investigations are needed to diagnose depression, but it is prudent to rule out general medical conditions that may mimic the symptoms of a depressive episode. The diagnostic interviews are too labor-intensive to make them suitable for population screening or for screening in primary care or other clinical settings. However, numerous brief screening instruments or questionnaires that are simple to administer and have reasonable clinical specificity and sensitivity have been developed (Table 4). Not all screening questionnaires are appropriate because of

the overlap of symptoms of depression and diabetes, including tiredness, lethargy, lack of energy, appetite changes, and sleeping difficulties. However, the Beck Depression Inventory (BDI), the Centre for Epidemiologic Studies Depression Scale (CED), the Patient Health Questionnaire (PHQ-9), and the Hospital Anxiety and Depression Scale (HADS) are all suitable for use in people with diabetes (22). Of these, the PHQ-9 is the best validated and most widely used in people with diabetes (125). It is also short, containing nine questions making it easy to administer in primary and secondary care settings. It has been suggested that the cut-off for major depression, which is ≥10 in primary care populations, should be increased by two points to ≥12 points in people with diabetes to help differentiate between diabetes-related symptoms and depressive symptoms (126).

Table 4. Reported sensitivity, specificity, positive and negative predictive value and reliability and validity in tools screening for depression in people with diabetes. Adapted from (22).

Tool	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Reliability/ Validity (α)
CES.	60.0 – 100	86.7	28.6	97.0	0.80
PHQ-9	66.0 - 100	52.0 - 80.0	43.8 - 64.4	93.4 - 100	0.80 - 0.84
BDI	82.0 - 90.0	84.0 - 89.0	59.0 - 89.0	82.0 - 97.0	
HADS	74.0 - 85.0	37.5 – 86.0	28.0 – 49.0	95.0 - 96.0	0.55 – 0.78

Sensitivity= Number of true positives (cases of depression)/Number of true positives + number of false negatives; Specificity = Number of true negatives/ Number of true negatives + false positives; Positive Predictive Value (PPV) = the proportion of cases with positive test results who are correctly diagnosed. Negative Predictive Value (NPV) = the proportion of cases with negative test results who are correctly diagnosed.

Another simple approach with good sensitivity and reasonable specificity is to ask two questions (127):

- During the past month, have you been bothered by having little interest or pleasure in doing things?
- During the past month, have you been bothered by feeling down, depressed, or hopeless?

If the answer to either is *yes*, and the person with diabetes wants helps with this problem, the healthcare professional should undertake a diagnostic interview and offer appropriate referral and treatment.

Although screening for depression is acceptable to people living with diabetes (128), its value has not been proven and remains controversial despite being recommended by several professional bodies, including the International Diabetes Federation (129), American Diabetes Association (130), and the UK National Institute for Health and Clinical Excellence (131). A 2008 Cochrane review reported that depression screening alone in the general population had little or no impact on the detection and management of depression (132). However, a more recent meta-analysis of depression screening interventions, many of which included additional components beyond screening, showed these were associated with less depression or depressive symptoms in the general population 6-12 months after screening (133). This issue is important because of the potential harms of screening, which include the stigma associated with depression, the risk of transient distress being labelled as having depression, and discrimination from insurance companies, and so studies demonstrating the effectiveness of screening in people with diabetes are needed.

Primary care depression screening in people with diabetes was introduced in the UK in 2006 as part of

the Quality and Outcomes Framework (a performance management and payment scheme for NHS general practitioners) with mixed results. In one semi-rural general practice, 365 of 435 eligible people with diabetes or ischemia heart disease were screened, but only three people without a current diagnosis of depression screened positive and none were subsequently diagnosed with depression (134). By contrast, in a study of 112 general practices in Leeds, UK, the rates of diagnosis of depression increased from 21 to 94 per 100,000 population per month after introduction of the screening compared with 27 to 77 per 100,000 population per month in people without screening (135). Despite the increased diagnosis, after an initial increase in antidepressant treatment, screening had little impact on prescribing habits.

Two clinical trials of depression screening in people with diabetes have not demonstrated a benefit. In the first study from the Netherlands, written feedback was provided to both the person with diabetes and the doctor following depression screening, but this did not change use of mental health services or improve depression scores compared with routine care (136). The second study from the USA examined the benefits of training healthcare technicians about the importance of discussing mental health with their patients (137). Although there was an improvement in depressive symptoms, this was no different from the control group and all the participants continued to have moderate to severe depressive symptoms.

Several reasons may explain the lack of effectiveness of depression screening in people with diabetes including a low acceptance of screening and subsequent referral to further care by people with diabetes, failure to screen those at highest risk of depression, reluctance by healthcare professionals, and generally poor quality of depression care in primary care systems (138). While identification of those with depression is an essential first step in treatment, screening alone will not improve clinical outcomes unless linked to appropriate care pathways and treatment (120, 139). By contrast, studies of care pathways that have clearly linked screening to diagnosis and treatment improved depression outcomes (140, 141).

Treatment of Depression

The main aims of treatment are to improve both mental health and diabetes outcomes (Table 5). Ideally, any depression treatment for people with diabetes would simultaneously improve both sets of outcomes, but from a clinical perspective, the rapid improvement or remission of depression should be the first priority (138). This recommendation partly reflects the time course of treatment responses, which can be seen within 2–4 weeks for depression but also because treating the depression may aid optimal diabetes self-management.

Table 5. Aims of Depression Treatment in People with Diabetes

Mental health outcomes	Diabetes outcomes
Decreased depressive symptoms	Optimal diabetes self-management
Remission of depression	Decreased HbA_{1c}
Suicide prevention	Increased time in glucose range
Improved health-related quality of life	Less hypoglycemia
Restoration of psychosocial functioning	Reduced long-term complications
	Reduced mortality

Until relatively recently, people with diabetes have been under-represented in trials of depression treatment and so, there were few studies examining antidepressant and psychological treatment of depression. However, over the last two decades, the evidence base for treatment has grown substantially and has clearly indicated that treatment with either psychological therapies or antidepressant medication is effective (142) .

PSYCHOLOGICAL TREATMENT

Various psychological treatments, including cognitive behavioral therapy, problem-solving, and psychodynamic techniques have been used to treat depression in people with diabetes. Different members of the healthcare team have been utilized to deliver these interventions in primary and secondary care either in person or virtually through the internet or telephone (142, 143). The majority of trials have included people with type 2 diabetes with no trials conducted solely in people with type 1 diabetes.

A meta-analysis of psychological treatments, including group-based and online therapies, reported they were effective for the treatment of depression with large effect sizes (142). The follow-up ranged between 4 weeks and 1 year and thus, the longer term effects are unknown. Cognitive behavioral therapy is the most studied intervention, with its core components being cognitive restructuring, behavioral activation, and problem solving. This intervention was judged to be moderately effective in two recent meta-analyses (144, 145). Mindfulness also has an moderate benefit in treating depression (146), but there is mixed evidence on the benefit of motivational interviewing in reducing depressive symptoms (147, 148). Although psychological treatments are better than no treatment, the rates of recovery are low post-psychological intervention (17% vs 9% in controls) (149), indicating that many people will need additional support if they are to recover fully from their depression.

There is more debate about the effect of psychological interventions on diabetes outcomes (138) with one systematic review reporting a reduction in HbA_{1c} of ~0.6 % (6 mmol/mol) (150) while another only reporting a non-significant improvement in glycemic levels (151). A meta-analysis of cognitive behavioral therapy showed a statistically significant but clinically insignificant reduction in HbA_{1c} of 0.14% (1 mmol/mol). There was a greater effect on HbA_{1c} if the intervention was delivered in a group-based and face-to-face fashion and included psycho-education, behavioral, cognitive, goal-setting, and homework assignment strategies as central components (145).

One of the challenges in delivering psychological interventions is the lack of trained personnel, a situation which appears to be worsening, at least in the United Kingdom (152). To address this deficiency, interventions have been designed to be delivered online or using mobile technologies, a trend which has increased dramatically since the Covid-19 pandemic. This has the potential to increase accessibility to treatment while limiting costs (142). One meta-analysis reported large effect sizes on depressive symptoms for online therapy and a moderate effect for telephone interventions, although no change in diabetes outcomes was seen (142). The beneficial effect on depressive symptoms up to 12 months after the interventions was supported by another systematic review, albeit again without improvement in diabetes outcomes (153). However, this finding was contradicted by a recent meta-analysis of 24 randomized controlled trials, 14 non-randomized controlled trials and three observational studies which reported no significant effect on depression outcomes (154). The discrepancy may partly explained by drop-out rates which vary from 13% to 42%; for those who remain in treatment, the interventions appear effective (155) and so the challenge will be to deliver services that engage people with diabetes and depression.

In the United Kingdom in 2008, the National Health Service introduced the Improving Access to

Psychological Therapies (now NHS Talking Therapies for anxiety and depression) program to improve the delivery of, and access to, psychological therapies for depression. By 2021/22, nearly 1.2 million people had accessed these services. Although the clinical workforce is appropriately trained and supervised, many practitioners do not have experience of the challenges of living with diabetes. To address this issue, the Southampton diabetes team has formed a partnership with the local NHS Talking Therapies service. A practitioner joins the multidisciplinary team in the young adult clinic once a fortnight, helping to engage the person with diabetes and facilitate referral and access to the service. There is also a wider benefit to the city as the NHS Talking Therapies team have become much more aware of the challenges of living with diabetes. Introducing this service led to reductions in depressive symptoms and diabetes distress and was well received by people with diabetes and staff alike (156).

ANTIDEPRESSANTS

Antidepressants have been used to treat depressive symptoms since the late 1950s. There are many different antidepressants, but these fall into five main categories:

- Selective Serotonin Reuptake Inhibitors (SSRI)
- Serotonin and Noradrenaline Reuptake Inhibitors (SNRI)
- Noradrenaline and Specific Serotoninergic Antidepressants (NASSA)
- Tricyclics (TCA)
- Monoamine Oxidase Inhibitors (MAOI)

The discovery of the first clinically useful antidepressants paved the way for an understanding of the underlying biological or neuroanatomical basis for depression. The first antidepressant was the tricyclic antidepressant (TCA), imipramine. It was first synthesized in 1951 as a potential antipsychotic and derived from work on chlorpromazine, which had pronounced sedative and antihistamine effects (157). Although imipramine has no antipsychotic effect, it was found to possess antidepressant effects. Other TCAs, such as amitriptyline, were subsequently synthesized by modifying the structure of imipramine. Iproniazid, a monoamine oxidase inhibitor (MAOI), was the next antidepressant to be discovered; again, this drug was initially developed for a different purpose, the treatment of tuberculosis, before its antidepressant effect was recognized. MAOIs prevent the breakdown of monoamine neurotransmitters (e.g. noradrenaline, dopamine and serotonin) while TCAs block the uptake of serotonin and noradrenaline resulting in an elevation of the synaptic concentrations of these transmitters. An understanding of the pharmacology led to the hypothesis that depression was caused by low catecholamine levels in the central nervous system (158). Both TCA and MAOI affect the serotonin system and in 1967, Coppen proposed that this was a more important neurotransmitter in depression than noradrenaline (159). Fluoxetine was the first in the class of selective serotonin re-uptake inhibitors (SSRI) and was developed by design following a search for molecules that could selectively block the re-uptake of serotonin. A major advantage of this approach was that it minimized adverse effects such as cardiovascular toxicity and anticholinergic effects. First synthesized in 1972 and launched in 1987, fluoxetine became the most widely prescribed drug in North America by 1990 (157). Although better tolerated than earlier antidepressants, SSRI still caused side effects, including sexual dysfunction, appetite change, nausea and vomiting, irritability, anxiety, insomnia, and headaches. In an attempt to reduce these adverse effects, other antidepressant classes were developed, including serotonin and noradrenaline reuptake inhibitors (SNRI, e.g. venlafaxine) and noradrenaline and specific serotoninergic antidepressants (NASSA, e.g. mirtazapine).

Antidepressants reduce depressive symptoms in people with diabetes as well as the general population; however, there have been relatively few formal efficacy trials in people with diabetes and even these

have been are limited to a small group of antidepressants, including fluoxetine, sertraline, paroxetine, citalopram, escitalopram, agomelatine, nortriptyline, and vortioxetine (138, 160). Furthermore, most studies are short-term and so the medium- and long-term sustainability of pharmacological interventions after treatment cessation is uncertain. A systematic review and meta-analysis suggested that all antidepressants have similarly large effect size on depression outcomes as long as adequate doses are used (151). However, a more recent network meta-analysis of 12 randomized controlled trials involving 792 participants reported that there may be a greater reduction in depressive symptoms with escitalopram and agomelatine (160). Vortioxetine was associated with the greatest reduction in HbA_{1c} with escitalopram, agomelatine, sertraline and fluoxetine also associated with a fall in HbA_{1c}. No antidepressant was found to disrupt glucose levels (160). These differences should be viewed with caution as the number of trials and participants for each drug is small. Further head-to-head randomized controlled trials would help us understand more about the relative benefits and safety of different antidepressants on depression and glucose metabolism.

Given the similar efficacy between antidepressants, the treatment of choice depends largely on the side-effect profile, individual preference, and response. SSRI are widely used as first-choice agents because they are less cardiotoxic than TCA and are safer in overdose. Some antidepressants, notably mirtazapine, paroxetine and some TCA, may cause undesirable weight gain (91) and should be used with caution in people with type 2 diabetes. By contrast, buproprion, which is available in the USA, is associated with weight loss and, unlike SSRIs, does not appear to worsen sexual function (161).

The aim of treatment is complete remission of depressive symptoms. Treatment should be maintained at an adequate dose for at least 4–6 months after remission of symptoms to reduce the risk of relapse and recurrence. Recovery from depression may lead to a change in the individual's behavior and routine which may have an effect on diabetes self-management. For example, if appetite improves, insulin requirements may increase, while on the other hand, if the person becomes more active, they may decrease. An individual approach is therefore needed to support the person's glycemic management. There are important drug–drug interactions between antidepressants and oral anti-diabetes agents through inhibition of the cytochrome P450 3A4 and 2C9 isoenzyme. For example, the use of fluoxetine may potentiate the effect of sulfonylureas precipitating hypoglycemia (84).

EXERCISE

Many depression guidelines recommend exercise and other aspects of a healthy lifestyle as an integral component of management. Coupled with the importance of exercise in glycemic management, interventions to increase physical activity have been trialed and shown to be effective in reducing depressive symptoms and improving glycemic measures (162).

PREVENTING SUICIDE

A detailed description of the many effective interventions to prevent suicide is beyond the scope of this article (163), however, it is important for diabetes healthcare professionals to understand how to identify those at risk, particularly given the high prevalence of suicidal ideation and acts and immediate availability of a means of suicide. It is crucial that suicide can be discussed with people with diabetes in a safe and non-judgmental way. Talking about suicide remains highly stigmatized and choosing to reveal suicidal ideation can be difficult. The isolation that suicidal people feel can be reinforced by a critical response from the healthcare team. A recent survey of diabetes healthcare professionals found that the vast majority of respondents believed it is their professional responsibility to ask about suicide and self-harm, with nearly half reporting that this should be addressed

every visit (164). Around three-quarters reported feeling comfortable discussing these issues, but those who were more reluctant to do so were concerned about their lack of training and uncertainty about what to do if someone reported self-harming behavior. Once an individual has discussed suicidal intention, it is important that the person is supported and has access to mental healthcare and suicide prevention interventions.

ORGANIZATION OF CARE

A common model of care of depression is the Stepped Care Model which provides a framework in which service delivery is organized to help those with depression, their caregivers, and healthcare professionals identify and access the most effective interventions (Figure 3) (131). The model utilizes a sequenced treatment process depending on the severity of depressive symptoms and response to previous treatments. The model allows a rational approach to the treatment of depression, while reducing costs and side effects of antidepressant through more appropriate prescribing.

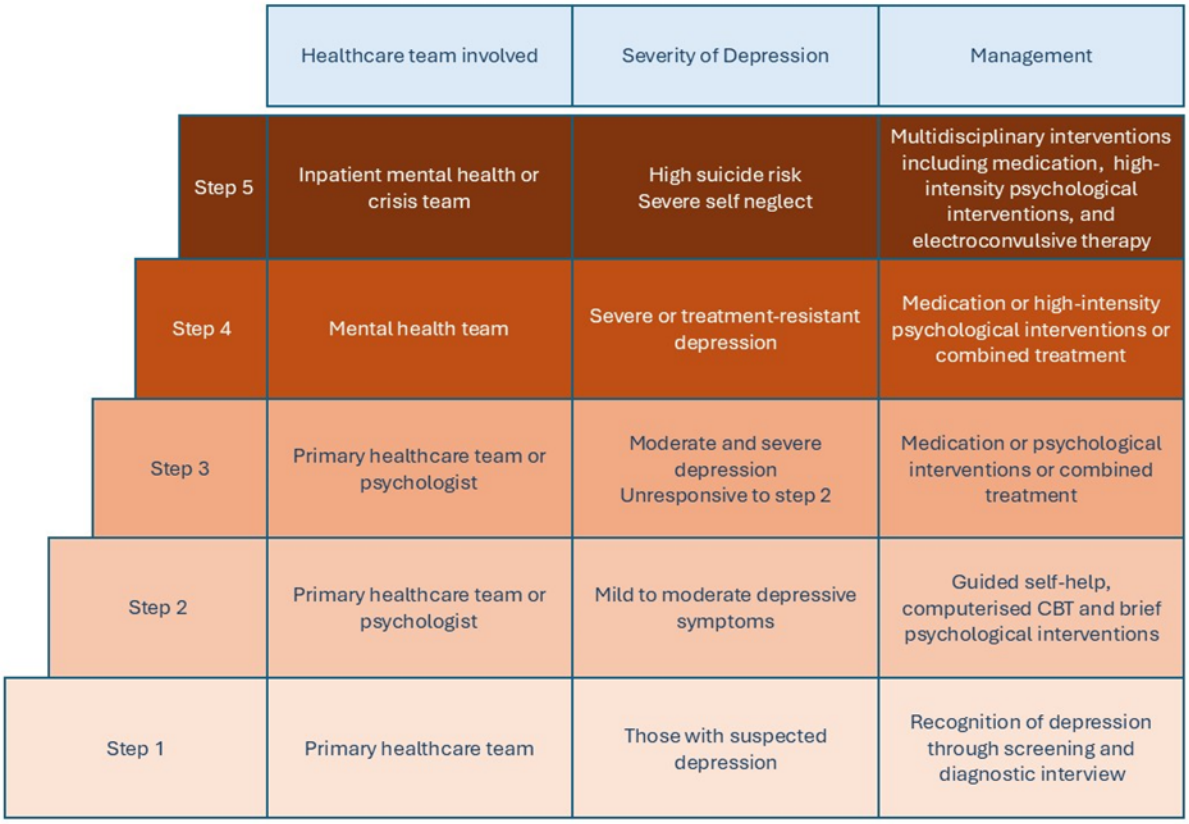

Figure 3. Stepped Care Model for management of depression (131).

The first step involves the recognition of depression through screening and diagnostic interview and is reserved for those with suspected depression. For those with mild depression, step 2 involves the use of guided self-help, computerized CBT, and brief psychological interventions which can be delivered by the primary healthcare team or psychologist. The third step, which is also delivered in primary care settings, is indicated for those who do not respond to step 2 interventions, or for those with moderate and severe depression. Treatments include medication, high-intensity psychological interventions, or combined treatment. Step 4 corresponds to severe or treatment-resistant depression; the interventions are similar to

those used in step 3 but now involve the mental health team. The final step is for those with life-threatening depression and/or severe self-neglect. In addition to medication and high-intensity psychological interventions, electroconvulsive therapy may be required under the supervision of a mental health crisis services and involve hospitalization.

A meta-analysis of 18 randomized controlled trial of stepped care showed improvements in depressive symptoms and better remission rates (165). A significant benefit on quality of life was also observed. More people in the stepped care model were prescribed antidepressants.

The increasing fragmentation of medical services and super-specialization in modern medicine has resulted in clinicians focusing on the conditions with which they are most familiar and being unable or unwilling to recognize and treat comorbid illnesses when they occur (166). The need for integrated holistic healthcare has never been greater but many diabetes healthcare professionals feel ill-equipped to manage depression. To address this, a case management model known as *collaborative care* was developed in the U.S., that involves a multidisciplinary team working together to identify and treat depression within primary care settings. The prototype intervention led to improvements in depression symptoms but without change in glycemia (167). Subsequently, greater attention was paid to intervention strategies for diabetes, resulting in simultaneous improvements in glycemic and blood pressure management and improved depressive symptoms (140). In a meta-analysis of five studies from the U.S., collaborative care was shown to be a clinical- and cost-effective treatment of depression, with a moderate effect size for depression outcomes and a small effect size for glycemic levels (142, 168).

CONCLUSION

Diabetes and depression remain a considerable clinical challenge. While an awareness of this co-morbidity has increased in recent years, this has not necessarily translated into better care or outcomes. Effective treatments are available and these need to be made available to those with diabetes and depression in clear treatment pathways. There are grounds for considerable optimism as the scientific knowledge that underpins clinical practices has expanded markedly in the last two decades. However, further research is needed to understand what can be done to prevent depression in people with diabetes and to identify the optimal treatment for an individual that improves both depressive symptoms and diabetes outcomes.

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