Diabetes, depression and cognitive disorders

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**Abstract**

The interactions between diabetes and the mind are complex: physical illness increases the risk of a number of psychiatric disorders, while mental illness and its treatment also alter the risks of diabetes and worsen both acute metabolic and long-term outcomes of diabetes.

The prevalence of depression is approximately 1.5 to 2-fold higher in people with diabetes compared with the general population. Approximately 10% of people with diabetes will have a formal diagnosis of depression and around a quarter have significant depressive symptoms. Microvascular and macrovascular complications and treatment with insulin are associated with higher rates of depressive symptoms. The underlying mechanisms are multifactorial and include genetic and environmental factors as well as disease and treatment effects. The presence of depression adversely affects diabetes outcomes; quality of life and glycaemic control are worsened while the rates of microvascular and macrovascular complications and mortality are increased in people with depression. Screening for depression in people with diabetes and prompt treatment, where necessary, is recommended.

Diabetes has modest effects certain aspects of cognition, including general intelligence, psychomotor speed, and mental flexibility, particularly when diagnosed in children under the age of 7 years.

Diabetes increases the risk of vascular dementia and Alzheimer’s disease, even after adjustment for traditional cardiovascular risk factors. Approximately 1 in 15 cases of dementia is attributable to diabetes. Insulin directly affects amyloid β formation. Dementia impedes the person with diabetes’ ability to self-manage their diabetes and mandates a change in glycaemic targets and management strategies.

Keywords: Diabetes, depression, diabetes-related distress, cognitive function, dementia, Alzheimer’s disease

**Introduction**

An effect of diabetes on the mind and vice versa has been recognised for many centuries; in the 17th century, Thomas Willis discussed how *“diabetes is a consequence of prolonged sorrow”* (1). As the brain is highly vascular and dependent on glucose for its normal functioning, it is perhaps unsurprising that diabetes affects cognitive function and the risk of mental illness. What is surprising is that clinicians looking after people with diabetes frequently ignore this association. Nevertheless, the effects of comorbid mental illness on someone with diabetes may be profound as the comorbidity worsens the clinical outcomes of both conditions. Quality of life across a broad range of domains is worsened, while the individual’s ability to self-manage their diabetes is impaired, ultimately leading to a higher incidence of complications and reduced life expectancy (2).

Despite the pressing clinical need to consider the comorbidity, in many countries, mental and physical health services are not properly integrated; this leaves diabetes services poorly equipped and organized to address both the physical and psychological needs of patients in the same setting (3). Over the last decade, however, there have been increasing levels of interest in the comorbidity from researchers, who have made considerable progress in understanding the epidemiology and underlying mechanisms explaining the association. This is beginning to change clinical practice with national and international guidelines highlighting the importance of assessing and treating the psychological sequelae of diabetes (4-6).

This chapter will first describe the complex relationship between diabetes and depression before considering the effects of diabetes on cognitive function, with particular reference to the association between diabetes and dementia.

**Diabetes and Depression**

Depression is a mood disorder, which is characterised by persistent low mood and loss of interest or pleasure in life. Other symptoms include weight loss or gain, change in sleep patterns, agitation or retardation, fatigue or loss of energy, feelings of worthlessness or guilt, diminished ability to think or concentrate and recurrent thoughts of death including suicidal ideation.

Depressive symptoms are common in the general population and vary considerably in severity. Consequently a clinical diagnosis of depression is defined by the number, severity and duration of symptoms; the most widely used diagnostic criteria in current practice are those of the Diagnostic and Statistical Manual of Mental Disorders 5th edition (7) (table 1). This degree of symptomatology is associated with significant disability and dysfunction, but it is important to recognise that less severe depressive symptoms may still adversely affect diabetes self-care and outcomes.

**Epidemiology of diabetes and depression**

Depression within the general population is common and its prevalence is increasing. It is predicted to become the second leading global cause of disability after heart disease by 2020 (8). The lifetime prevalence varies widely across the globe from 3% in Japan to 17% in the USA, falling between 8-12% in most countries. At any one time, approximately 3-5% of men and 8-10% of women have depression. Given the high prevalence of diabetes and depression, one would expect a degree of comorbidity but the current evidence suggests that depression occurs more frequently in people with diabetes and vice versa than would be expected by chance (9).

Recent meta-analyses have demonstrated that significant depressive symptoms affect approximately 1 in 3-4 adults with diabetes while a formal diagnosis of depressive disorders is made in approximately 10-15%, equivalent to a 1.5-2.0 fold increased prevalence (10;11). Longitudinal cohort studies report the incidence of depression to be 15-24% higher in people with diabetes compared with those without diabetes (12;13). On the other hand, the incidence of type 2 diabetes is also increased by 15-37% among people with depression (13;14), indicating the bi-directional nature of the relationship between these conditions. Episodes of depression appear to be more persistent and more likely to relapse among people with diabetes (15), which may in part explain the discrepancy between the relative incidence and prevalence figures.

Although the literature is consistent in showing an increased prevalence of depression in people with diabetes and vice versa, within each of the meta-analyses, there is considerable variation in risk estimates. This variation stems in part from the meaning of the word “*depression*”, which spans from relatively minor, occasional negative mood symptoms to life-threatening disabling conditions (9). More recently, papers have started to differentiate between “*depressive symptoms*” and “*depression*” and this change in definition partly explains why current risk estimates of “*depression*” are lower than former ones. Another reason why earlier studies reported higher prevalence rates is because the studies recruited selected patient populations, often drawing from specialist diabetes clinics, where referral patterns and other differences in demographic characteristics, such as ethnicity, may increase the likelihood of depression.

The gold standard diagnostic procedure is a diagnostic interview, such as the Structured Clinical Interview for DSM-IV-TR Axis I Disorders SCID interview (16) or the Schedule for Clinical Assessment in Neuropsychiatry 2.1 (17), but these are time-consuming and are unfeasible in most large epidemiological studies. Consequently, many studies have relied on self-rating scores, which tend to overestimate the true prevalence of depression and only provide an estimate of true caseness. These questionnaires may further exaggerate the prevalence of depression because of the overlap of the symptoms of diabetes and depression (18).

**Depression or distress**

Some authors have argued that much of the psychopathology previously identified as depression is in fact ‘diabetes-related distress’ (19). This concept captures the emotional distress associated with living with diabetes (20), with the top most frequently reported problems including:

* ‘worries about the future and the possibility of serious complications’,
* ‘feeling guilty or anxious when you get off track with your diabetes management’,
* ‘feeling scared when you think about living with diabetes’,
* ‘feeling discouraged with your diabetes regimen’ and
* ‘feeling depressed with you think about living with diabetes’.

These symptoms are recognised in up to 60% of people with type 1 diabetes or insulin-treated type 2 diabetes (21;22) and are negatively associated with diabetes self-care and optimal glycaemic control (21). Indeed HbA1c correlates more closely with diabetes-related distress than depression. These feelings are more likely to develop in those with long-standing diabetes and in those with recurrent severe hypoglycaemia. Given the commonality of some symptoms, e.g. low mood and guilt, it is unsurprising that many people are reported to display both diabetes-related distress and depressive symptoms with ~30% overlapping variance. Nevertheless as well as the distinct association with glycaemic control, the association with self-management also differs between distress and depression, strengthening the view that these are two distinct entities.

**Specific Populations**

Many studies examining the prevalence of depression in people with diabetes have not differentiated between the type of diabetes. This limitation is important because people with type 2 diabetes are generally older and depression prevalence varies with age, the rates of various diabetic complications and other co-morbid conditions (e.g. obesity, heart disease) differ and management strategies are different. Because the prevalence of type 1 diabetes is so much lower than type 2 diabetes, people with type 1 diabetes are under-represented in depression association studies. One review of depression in type 1 diabetes (23), however, reported that depression was present in 12%, compared with 3.2% in people without diabetes. However, if studies without control groups and interview ascertainment were excluded, the estimated prevalence fell to 7.8%, which was no longer statistically significantly different from people without diabetes (OR 2.4, 95% CI -0.7 to 5.4). A recent study of 368 individuals with type 1 diabetes found an unexpectedly low rate of major depressive disorder (3.5%) and highlighted the marked difference in estimated prevalence rates using self-rated questionnaires (11.4%) compared with diagnostic interviews, again perhaps reflecting an effect of the overlap with diabetes-related distress (19).

Although many of the early studies were undertaken in Western Europe and North America, a recent report including 231,797 adults from 47 countries using data from the World Health Organisation World Health Survey found a two-fold increase in episodes of depressive symptoms in people with diabetes living in South America, Asia and Europe (table 2) (24). No increase in depressive symptoms was seen in people living in Africa but this may reflect less complete case ascertainment because of cultural differences in the understanding of depression.

Although there are few data, depression rates (9-26%) also appear elevated in children and adolescents with diabetes (9).

**Aetiology of diabetes and depression**

**Which people with diabetes are at risk of depression?**

Female sex, marital status, childhood adversity and social deprivation are all risk factors for depression in otherwise healthy individuals and these appear to operate equally in people with diabetes. However, in addition, there are a number of diabetes specific and treatment risk factors associated with the development of depression.

Poor glycaemic control and recurrent hypoglycaemia are risk factors for depression, in part as a direct effect of hypoglycaemia and hyperglycaemia on brain function as well as the psychological effects of abnormal glucose levels. Animal models of diabetes have loss of hippocampal integrity and neurogenesis (25), while hippocampal atrophy has also been shown in MRI studies of people with diabetes (26). These structural changes are associated with neurotransmitter abnormalities, including increased prefrontal glutamate-glutamine-gamma-aminobutyric acid levels, which have been observed in people with type 1 diabetes in a manner that correlates with mild depressive symptoms.

Diabetes is not the only chronic physical condition associated with the development of depression, which occurs also more commonly in people with cardiovascular disease (27), cancer (28) and inflammatory arthropathies among others (29). As disease burden increases, so does the prevalence of depressive symptoms. It is therefore unsurprising that depressive symptoms are more common in people with diabetes who have developed either macrovascular or microvascular complications (30). In a specialized outpatient clinic, people with two or more diabetes complications had twice the risk of depression, with neuropathy and nephropathy showing the strongest association with depression (31). Sexual dysfunction and painful peripheral neuropathy also appear to be particularly associated with depression (30).

People with insulin treated type 2 diabetes have higher rates of depression compared to those treated with lifestyle interventions or non-insulin medications (32;33). Exactly why this is the case is uncertain but probably has more to do with the increased treatment demands including intensive self-monitoring of blood glucose, longer duration of disease and higher rates of diabetes complications than a direct effect of insulin *per se* (33).

**Why do people with diabetes develop depression?**

The traditional view is that people with diabetes develop depression because of the psychological response to living with a chronic condition that is associated with unpleasant consequences and treatment that places heavy behavioural demands on the individual. There is support for this hypothesis as a meta-analysis indicated that the rates of depression were only increased among people with diagnosed diabetes while those with undiagnosed diabetes or impaired glucose regulation had no difference in depressive symptoms compared to those with normal glucose metabolism (34). This finding is important for clinicians who have the responsibility of communicating the diagnosis and its implications to people with new onset diabetes in a sensitive and compassionate manner to help people adjust to the diagnosis.

According to one German study, adults with new onset type 1 diabetes were more than twice as likely to develop a major depressive episode (5.8% vs 2.7%), although the difference was only statistically significant in women (35). By contrast, the situation appears less clear cut in people with type 2 diabetes where several studies have shown that the diagnosis has little impact on well-being (36;37); the higher rates of depression only start to appear as the disease moves from being asymptomatic to one where complications begin to occur and where treatment demands increase.

This psychological model does not preclude other biological mechanisms and it is important to recognise that acute changes in glucose may lead to a change in mood (38). Whether long-term changes or glucose variability may trigger depression directly is uncertain but changes in brain structure and function have been seen in the areas responsible for mood in people with type 1 diabetes (26).

**Why do people with depression develop diabetes?**

The low mood and loss of interest in pleasurable activities may lead to changes in behaviour that increase the risk of diabetes. People with depression tend to eat less prudent diets (comfort eating is a readily understandable concept), are less likely to undertake regular physical activity and are more likely to be smokers, all of which increase the risk of diabetes (39-41).

Depression is associated with poorer self-care management. This has been studied in more depth in people with established diabetes when people with comorbid depression are more likely to miss medical appointments and are less likely to follow advice about medication use, glucose monitoring and foot care (42). In people with established diabetes, this is associated with poorer diabetes outcomes but if similar patterns of behaviour pre-dated the diagnosis of diabetes, this may have contributed to its onset.

Several biological changes occur in depression, including alterations in the hypothalamic pituitary axis (HPA) and inflammatory markers that could lead to increased insulin resistance and consequently risk of diabetes (43). Subclinical hypercortisolism, blunted diurnal cortisol rhythm, or hypocortisolism with impaired glucocorticoid sensitivity have all been observed in depression while inflammatory changes include elevated concentrations of C-reactive protein, TNF-α and proinflammatory cytokines, which have been implicated in causing sickness behaviour in animal models and depression in humans (44;45). Disrupted sleep, which is common in depression, may be a further biological mechanism linking to diabetes as poor sleep quality and altered circadian rhythms are associated with an increased risk of diabetes through insulin resistances (46).

There have been concerns that the use of at least some antidepressants may worsen the risk of diabetes (47) as substantial weight gain may occur with certain antidepressants, including mirtazapine, amitriptyline and paroxetine (48). Case reports and early observational studies demonstrated a consistent association between antidepressant usage and risk of diabetes; however, more recent cohort studies have shown much lower odds ratios, to the point where the association could be explained by confounding and the antidepressant use is merely a marker of individuals at high risk of diabetes. Randomized controlled trials have reported both hyperglycaemic and hypoglycaemic effects suggesting that not all antidepressants are alike (47).

**Do common antecedents explain the association between diabetes and depression?**

Both diabetes and depression occur more frequently among people from lower socio-economic classes raising the possibility that both conditions occur because of shared environmental risk factors. The importance of social status was demonstrated in a recent study from Denmark, which showed that, while all people with diabetes were more likely to develop depression than those without diabetes, those from lower employment and income groups were disproportionately affected (49).

It is uncertain how the adult environment increases the risk of diabetes but poor physical (e.g. traffic, noise, decreased walkability) and social environments (e.g. lower social cohesion, increased violence, decreased residential stability) are associated with worse diet and lower physical activity levels that predispose to obesity, diabetes and depression (50). Although it is impossible to determine causality from these observational studies, dysfunctional HPA axis activity and disruption of its normal circadian rhythm (i.e. blunted profile) (51-55) as well as enhanced inflammation have all been observed in people living in adverse neighbourhood environments providing a potential biological mechanism to explain the association (56;57). Similar mechanisms may also operate in childhood adversity.

An adverse fetal environment may also predispose an individual to both type 2 diabetes and depression. There is a J-shaped relationship between birth weight and plasma glucose, insulin concentrations and type 2 diabetes while some but not all studies have shown that fetal under-nutrition is associated with adult depression (9). Again programming of the HPA axis may be one biological mechanism to explain the association (43).

**Consequences of depression in diabetes**

People with comorbid depression experience worsened diabetes outcomes and poorer quality of life (58-60). While it is clear that those with microvascular complications are more likely to develop depression, recent work has also shown that those with depression are more likely to develop complications. In one 10-year cohort study of individuals with childhood-onset diabetes, in addition to longer duration of diabetes and poor glycaemic control, the overall proportion of time that an individual was depressed predicted retinopathy severity (61). Similarly, in a longitudinal study of people with type 2 diabetes, progression to diabetic retinopathy and to proliferative diabetic retinopathy was more likely in those with high depressive symptom scores at both baseline and 6-year follow-up (62). Depression may worsen the pain experienced by those with painful peripheral neuropathy (63). Poor glycaemic control is not the explanation for the increase in microvascular complications seen in people with comorbid depression as studies have not reported a consistent association between depressive symptoms and HbA1c (64-66). Nevertheless, impaired self-care among people with depression may play a role.

Cardiovascular morbidity and mortality is increased in people with comorbid diabetes and depression (67); in one study those with diabetes and depression has an annual mortality rate of 8%, which was 2.5 fold higher than those without either condition (68).

**Management of people with diabetes and depression**

A greater awareness of the link between diabetes and depression have led several national and international guideline bodies to recommend action to improve the psychological well-being of people with diabetes (4-6). There is a responsibility for healthcare professionals caring for those with diabetes to identify depression when it occurs and then institute prompt treatment in order to reduce depressive symptoms and to improve self-care, glycaemic control and diabetes outcomes (69).

**Screening and diagnosis of Depression**

It goes without saying that before treatment can be offered, depression must be recognised and diagnosed. A formal diagnosis of depression requires a time consuming validated interview and so this is impractical for routine clinical care. Consequently, quicker and cheaper screening methods are needs to identify those in primary and secondary care with depressive symptoms who should then go forward for a diagnostic interview (70).

Many easy-to-use questionnaires that can be self-completed have been developed for routine use in clinical care but because of the overlap between symptoms of diabetes and depression, only validated questionnaires should be used for people with diabetes (18). The Patient Health Question-9 (PHQ-9), which contains 9 questions, is the most widely used and validated questionnaire in type 2 diabetes but even this overestimates the prevalence of depression (19). A score of ≥10 reliably identifies those with major depression is in community populations but a higher cut-off of ≥12 has been suggested for people with diabetes in order to improve the discrimination between diabetes related symptoms and depressive symptoms (71). The Beck Depression Inventory, the Centre for Epidemiologic Studies Depression Scale and the Hospital Anxiety and Depression Scale (HADS) are other examples of well-validated questionnaires for people with diabetes.

An even simpler approach that can be used by diabetes healthcare professionals is to ask two questions:

* “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,” the healthcare professional should ask patient if they want help with this problem. If the answer to this is also “yes,” a diagnostic interview should be undertaken followed by appropriate referral and treatment.

Although diagnosis of depression is necessary to instigate treatment, there is debate as to whether screening for depression should be undertaken (70). Depression screening in the general population has little or no impact on the detection and management of depression if used alone and robust clinical pathways are essential to ensure that appropriate treatment can be offered if a diagnosis is made (72). The importance of this in the context of diabetes was demonstrated in a Dutch randomized controlled trial, which investigated the benefits of depression screening in people with type 2 diabetes (73). Following screening, although written feedback was provided to both participant and doctor, neither utilisation of mental health services nor depression scores improved. A further study from the USA also failed to demonstrate any improvement in depressive symptoms despite a modest increase in mental health care utilization (74). 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 to undertake screening and treatment and generally poor quality of depression care in primary care systems may all contribute to these findings (69).

Thus, while there is a strong imperative to identify people with depression, better integration with care pathways is needed, before screening can be wholeheartedly adopted, not least because screening without appropriate follow-up could lead to harm, by increasing the stigma and discrimination associated with depression and the risk of labelling transient distress as illness (69).

**Treatment of depression in people with diabetes**

As depression adversely affects psychological well-being and diabetes outcomes, the best treatment approaches focus on both improving depressive symptoms and diabetes self-management. The aim of depression treatment is to achieve complete remission of symptoms with the further goals of improving health-related quality of life and psychosocial functioning (69). Over the last decade, a number of randomized controlled trials have demonstrated the effectiveness of both psychological and pharmacological treatments of depression in people with diabetes (69). Most of these trials have been undertaken in people with type 2 diabetes and so there is still a paucity of evidence for type 1 diabetes.

**Psychological treatment**

Psychological interventions are heterogeneous incorporating various techniques (e.g. cognitive behavioural therapy, problem-solving and psychodynamic), different settings (primary and secondary care) and media (face-to-face, group, web based and telephone contacts) (69). Given this level of variability, it is perhaps unsurprising that the effectiveness of interventions differs and comparisons between trials are challenging. Nevertheless, meta-analyses suggest psychological interventions improve depressive symptoms, with a moderate to large effect size (standardised mean difference (SMD) ranging from -0·14 to -1·47). The effect on glycaemic control, however, is more modest with one systematic review reporting a reduced HbA1c of ~0.6% (6 mmol/mol) (75) and another indicating a non-significant improvement (SMDs from 0.40 to –1.40) (76). Four recent trials on psychological interventions found an improvements in glycaemic control (SMD -0.25 to -0.68) (69). Web-based psychological therapies appear less effective than face-to-face contact, particularly for glycaemic outcomes (77). The most effective psychological interventions combine diabetes self-management education with psychological support (78).

**Pharmacotherapy**

There are several classes of effective and well-tolerated antidepressants and these form an integral component of depression management. Randomised clinical trials in people with diabetes have been undertaken for only a relatively small group of antidepressants, including nortriptyline, fluoxetine, buproprion, sertraline, paroxetine, and citalopram (69); however, these trials show that these antidepressants improve depressive symptoms to a similar extent in people with diabetes and the general population. All antidepressants studied appear to have similar efficacy and as long as adequate doses are used, the effect sizes are ‑0.61 SMD (76). However, there are gaps in our evidence base, with regards to glycaemic control and the medium- and long-term sustainability of pharmacological interventions after treatment cessation. Furthermore, a number of new antidepressants have recently been approved, including vilazodone, vortioxetine, and levomilnacipran, which have not been formally assessed in people with diabetes.

Given the comparable effectiveness, the treatment of choice depends largely on the side effect profile, patient preference and individual response. Selective serotonin reuptake inhibitors (SSRIs) are widely regarded as first choice agents because they are less cardiotoxic than the older tricyclic antidepressants and are safer in overdose.

Some antidepressants, including mirtazapine, paroxetine and some tricyclic antidepressants, may cause unwanted weight gain (48) while buproprion, which is available in the USA but not Europe, is associated with weight loss.

Several antidepressants may interact with oral hypoglycaemic agents through inhibition of the cytochrome P450 3A4 and 2C9 isoenzyme. For example, the use of fluoxetine may potentiate the effect of sulfonylureas precipitating hypoglycaemia (79).

Antidepressant treatment should be continued at an adequate dose for at least 4-6 months after complete remission of depressive symptoms to reduce the risk of relapse and recurrence. This is particularly important in people with diabetes, in whom the risk of relapse and persistence of symptoms is greater than the general population.

Clinical trials demonstrate that SSRIs lead to a modest improvement in glycaemic control (SMD -0.38) but there is a mixed effect on glycaemic control with other antidepressants ranging from hyperglycaemic effects with tricyclic antidepressant medications to euglycaemic or slightly hypoglycaemic effects with serotonin–noradrenaline reuptake inhibitors. The diversity of effect implies that any finding of improved glycaemic control with individual antidepressants should not be extrapolated to other untried antidepressants (69).

The treatment of depression may lead to a change in the patient’s behaviour and routine requiring a change in diabetes self-management. For example, should the patient’s appetite improve, more insulin may be required; by contrast, if the patient becomes more physical active, less may be needed.

**Models of Care**

Many health care systems are poorly equipped to manage comorbidity, particularly where this involves mental and physical illness. The Cartesian split of mind and body affects the delivery of care, leading healthcare professionals to consider one or other illness rather than making holistic decisions. In order to overcome this, the late Wayne Katon and colleagues in Seattle pioneered a model of care, known as “Collaborative Care” (80). This model encourages interdisciplinary cooperation between health care providers and shared decision making to facilitate appropriate provision of evidence-based treatment options, regular follow-up, self-management training and support for people with co-morbid diabetes and depression. The first study of this model showed improvements in depression symptoms but no change in glycaemic control (81); however, in later studies, greater attention was paid to diabetes and blood pressure interventions, leading to improved biomedical outcomes as well as improved depressive symptoms (80). These models of care are also highly cost-effective (82;83).

**Cognitive Function**

Cognitive function can be defined as an intellectual process by which one becomes aware of, perceives, or comprehends ideas. It involves aspects of perception, thinking, reasoning, and remembering. Given the multifaceted nature of cognition, a full assessment of cognitive functioning requires a battery of psychometric tests to obtain an overview of an individual's thinking skills. These tests assess how a person processes information, reasons and learns in different ways. Cognitive function may be impaired globally or specific components of cognitive function may be affected.

**Diabetes and cognition**

As cognitive and affective processes occur in highly linked regions of the brain, it is unsurprising that people with diabetes also experience cognitive deficits. These are relatively modest in most individuals but particularly affect general intelligence, psychomotor speed, and mental flexibility; on average performance in these domains is 0.3 – 0.7 standard deviations below the population mean (84-86) and has been likened to the change in cognitive function experienced after a 6-8 hour jetlag (figure 1). The effects of diabetes on the brain appear to be age related with children and older adults being most vulnerable, with effects being attributable to both hypoglycaemia and chronic hyperglycaemia.

**Cognitive dysfunction in children and adolescents**

The age of onset of diabetes is a major determining factor for its effect on cognitive function in children. In those diagnosed before the age of 7 years, there is an increased risk of developing cognitive impairment across a range of cognitive domains, including attention, mental flexibility, psychomotor efficiency, learning, memory, problem-solving and overall intelligence, and which start to be apparent within 2-3 years of diagnosis (87-91). For children diagnosed after this age, the effect is much more modest and is confined primarily to overall intelligence and speed related tasks, particularly those with a visual-perceptual aspect (88). The cognitive impairment seen in children diagnosed before the age of 7 years persists into adulthood and manifests as lower IQ scores and slower information processing (92).

Academic achievement is lower in children with diabetes, irrespective of the age of diagnosis but this could relate to school absences or hypoglycaemia interfering with learning as much as a direct effect on the developing brain (93). However, there is evidence from older studies that severe hypoglycaemia causes neuropsychological deficits, particularly in children whose onset of diabetes occurred below the age of 6 years (94;95). Part of the problem is that younger children may not be able to describe their hypoglycaemic symptoms thereby increasing the likelihood of prolonged and severe hypoglycaemia. Some support for the hypoglycaemia hypothesis comes from a meta-analysis of data from 441 children with recurrent severe hypoglycaemia and 560 children without recurrent severe hypoglycaemia (96). This study found that those with recurrent severe hypoglycaemia had a modestly reduced performance in the domains of intelligence, language and memory and learning but motor speed was unaffected (96). This effect appears to be limited to children because there was no difference in the cognitive function in adults with type 1 diabetes in the Diabetes Control and Complications Trial with and without a history of severe hypoglycemia after an 18-years follow-up period (97). Similarly, the ACCORD MIND study, which recruited adults with type 2 diabetes, found no difference in cognitive function after 20 months and 40 months follow-up between those treated intensively compared with standard care despite a three-fold increase in the rates of hypoglycaemia (98).

**Cognitive dysfunction in adults with diabetes**

Adults with type 1 diabetes show modest non-progressive cognitive deficits in measures of intelligence, attention, psychomotor speed, cognitive flexibility and visual perception but measures of language, learning and memory are unaffected despite long duration of diabetes (85;99). With the exception of “crystallized intelligence”, the affected domains require a rapid response indicating that diabetes affects mental agility rather than accuracy.

These changes are accompanied by structural changes that are characterised by reduced grey matter volumes in the frontal lobe and the adjacent supramarginal and postcentral gyri (100). These MRI alterations have been linked to disrupted integrity of fibre tracts connecting the main cortical areas of the brain (101). Functional studies have demonstrated altered cerebral perfusion with both decrease and increased blood flow (102-104).

Adults with type 2 diabetes also show mild cognitive deficits affecting memory, processing speed, and executive function, which may lead to the individual to be less able to process unstructured information (84;86). Interestingly similar deficits are also present in people with newly diagnosed type 2 diabetes and impaired glucose regulation as well as those with features of the metabolic syndrome (105-107). Type 2 diabetes is also associated with structural changes in the brain, characterised by a loss of grey matter loss in the medial temporal, anterior cingulate, and medial frontal lobes, while white matter is lost in the frontal and temporal regions (108).

The mechanisms underlying these changes are not fully understood although studies have not consistently demonstrated an association with cerebral small vessel disease (101). The link between glycaemic control and cognitive dysfunction in adults with diabetes is less obvious than for children. As previously described, hypoglycaemia does not appear to be a major risk factor for cognitive decline in young and middle aged adults with diabetes but hyperglycaemia appears to be more important, at least in the case of type 1 diabetes. A recent meta-analysis found a weak negative association between HbA1c and cognitive function, with HbA1c explaining at most 10-15% of the variance in cognitive function (109).

The presence of microvascular complications, especially retinopathy and nephropathy, is associated with accelerated cognitive decline (110;111). Cardiovascular disease and its risk factors are also associated with cognitive decline as they are in the general population but whether there is any specific interaction with diabetes is uncertain (101;110).

**Dementia**

The term dementia encompasses a broad category of brain disorders that lead to a gradual and progressive decline in cognitive function to the extent that an individual’s ability to function on a day-to-day is impaired. There are a number of types of dementia of which the most common are Alzheimer’s disease (50-70% of cases) and vascular dementia (up to 25%). Other causes of dementia are shown in table 3. There has been a rapid increase in the prevalence of dementia in recent years, with a global prevalence of 22.7 million in 2015. The World Alzheimer Report predicts the prevalence of dementia to rise to 38.5 million by 2030 and 131.5 million by 2050. This increase is largely being driven by an ageing population as the prevalence rises from 1.4% in men and 1.9% in women aged 60-64 years to 33.4% in men and 48.3% in women aged >90 years. In 2013, approximately 1.7 million people died as a result of dementia.

**Diabetes and Dementia**

The rate of cognitive decline in older individuals with type 2 diabetes appears to be up to two-fold quicker than the general population and a number of studies have indicated that the risk of dementia is increased by approximately 50% in people with diabetes (112). The commonest cause of dementia in people with diabetes is Alzheimer’s disease, which is increased by 46%, while vascular dementia is increased 2.38 fold (112). It is estimated that the diabetes-attributable risk of dementia is 6-7%; in other words, 1 in 15 cases of dementia is attributable to diabetes (101). An increased risk of dementia has also been reported in people with pre-diabetes and metabolic syndrome (105). Diabetes worsens the outcome for people with dementia and is associated with 90% increase in mortality compared with those without diabetes (113).

Part of the explanation for this increased incidence of dementia risk stems from a higher prevalence of risk factors for dementia among people with diabetes (Table 4). Many of these cardiovascular risk cluster in people with diabetes and those at risk of diabetes. Interestingly glycaemia *per se* appears to have little impact on the risk (109). Only one study has linked elevated HbA1c with the risk of dementia and only in those with markedly elevated levels (10-12%, 86 – 108 mmol/mol). No association between fasting or post-prandial glucose or measures of glucose variability with dementia has been found.

Unlike in younger adults, recurrent hypoglycaemia is an important risk factor for cognitive decline in those with dementia (114;115). In a retrospective study of 16,667 older people with diabetes, a history of one, two and three or more severe hypoglycaemic episodes increased the risk of dementia increased by 26%, 80% and 94% respectively independent of glycaemic control, medications and other comorbidities (114). The relationship, however, appears to be bi-directional as cognitive dysfunction increases risk of hypoglycaemia, thereby creating a vicious cycle.

Impaired insulin signalling in the brain may also play a role in the development of Alzheimer’s disease (116). Briefly, the pathology of Alzheimer’s disease is characterised by the deposition of β-amyloid plaques and tangles in the brain (117;118). β-amyloid is derived from the cleavage of amyloid precursor protein, an extracellular protein which is critical to neurone growth, survival and post-injury repair. The formation of β-amyloid is regulated with several genes but is increased in ageing and by obesity and less prudent diet (118). Insulin inhibits the production and accumulation of β-amyloid and so in situations where there is insulin deficiency or impaired action, β-amyloid accumulates (116). Supporting this hypothesis is the observation of reduced brain insulin and its receptor in people with Alzheimer’s disease.

**Clinical Implications of Dementia in people with diabetes**

**Prevention of dementia**

Several large randomised controlled trials in both type 1 diabetes and type 2 diabetes have investigated whether improved glycaemic control can reduce the risk of dementia. To date, no difference in the rate of cognitive decline, cognitive performance or incidence of dementia has been seen in those with tighter glycaemic control (97;98;119;120). The ACCORD-MIND study also assessed whether better blood pressure and lipid control could improve cognition but again no benefit was seen in those treated with a combination of statin and fibrate while intensive blood pressure lowering actually accelerated brain atrophy (121).

**Diagnosis of dementia**

Once dementia develops, the person’s ability to self-manage their diabetes progressively deteriorates. Exercise and diet appear to be particularly affected but the real danger lies in the increased risk of adverse events in people taking hypoglycaemic drugs. The risk of hypoglycaemia is exacerbated further because dementia may impair language and lead to disorientation and personality changes, all of which may mimic the symptoms of hypoglycaemia (122). When lack of engagement with self-management occurs in older people, clinicians should consider cognitive dysfunction as a cause.

A risk score which includes age, microvascular disease, diabetic foot, cerebrovascular disease, cardiovascular disease, acute metabolic events, depression and education, has been developed to help predict the risk of developing dementia. In a prospective study over 10 years, the risk of developing dementia was 5.3% in those with the lowest score compared with 73.3% for the top scores (123). Other authors have advocated the use of the easy-to-perform Mini Cog test as a simple screening tool for dementia. This test has a sensitivity of 86.4% and a specificity of 91.1% (124).

A formal diagnosis of dementia involves a combination of history, examination, including tests of mental investigation and investigation. It is important to obtain corroborating information from a friend or relative who knows the patient well. Unfortunately, the diagnosis is not always straightforward particularly in the early stages and time may be an important diagnostic tool.

**Treatment of dementia**

A detailed description of the treatment of Alzheimer’s disease is beyond the scope of this chapter as treatment is usually initiated in specialist memory clinics. The most commonly used drugs are the acetylcholinesterase inhibitors, such as donepezil, which are licensed for the treatment of mild to moderate Alzheimer’s disease (125). This class of agents can cause bradycardia and exacerbate symptoms of gastric and duodenal ulcers, precipitate bronchospasm and may cause convulsions. Dizziness, headache and nausea are the most common side effects with abdominal disturbance and nightmares also commonly reported. Because of the cardiovascular effects, they should be used with caution in those whose baseline pulse is <60 beats per minute. An ECG is recommended if the pulse is <70 beats per minute or if it is irregular.

Given the relationship between cerebral insulin action and Alzheimer’s disease, the use of several anti-diabetes drugs has been examined in people with dementia (101;116). Small studies have suggested that intra-nasal insulin improves delayed memory and cognitive function (126;127) but the results of larger on-going trials people with Alzheimer’s disease, with and without diabetes are awaited (101). Studies of thiazolidinediones have shown mixed effects on cognitive function but a possible benefit has been reported in those whose genotype is APOE-ε4-negative (128-130). As well as insulin, GLP-1 also appears to play an important role in the control of synaptic plasticity and in some forms of memory formation and two trials of GLP-1 receptor agonists are on-going (116).

**Management of diabetes in someone with dementia**

As dementia affects self-management, it is important that glycaemic targets are adjusted appropriately taking into account overall health and life expectancy. Several guidelines now recommend HbA1c targets of <8.5% (69 mmol/mol) for older dependent people with dementia (131). In these individuals, avoidance of symptomatic hypoglycaemia is more important than tight glycaemic control, which may reduce the quality of life. Glycaemic targets should be regularly reviewed and medications as appropriate.

Many older people with diabetes and dementia are over-treated with multiple drugs. In a retrospective cohort study of 15,880 people with type 2 diabetes and dementia from the Veterans Affairs Healthcare System, 52% of participants had an HbA1c <7% (53 mmol/mol) and within this group, 75% were treated either with sulfonylureas, insulin or both placing them at a high risk of hypoglycaemia (132). Declining weight, malnutrition and frailty may lead to a reduced need for antidiabetes medications and these have been safely withdrawn in several studies (133) without a deterioration of their glycaemic control (134). Drugs with a lower risk of hypoglycaemia should be preferentially used.

**Conclusions**

This chapter has highlighted some of the many and various ways in which diabetes interacts with the brain. It is clear that these connections can have a major impact on diabetes outcomes, and health professionals who work with people with diabetes requiregood knowledge and awareness of these issues to be able to provide optimal care. There is clearly also a great need for closerworking between diabetes services and mental health services while further research on these topics is also required.

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**Conflict of Interest**

RH has received fees for lecturing and consultancy from the following companies: Eli Lilly, Janssen, Lundbeck, Novo Nordisk, Novartis, Otsuka, Sanofi, Takeda, MSD.

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**Tables**

Table 1. The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) Definition of a “Major” Depressive Episode

1. 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.
1. The symptoms cause clinically significant distress or impairment in social, occupational or other important areas of functioning.
2. 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).

**Table 2: Increased risk of depressive episodes in people with and without diabetes in four continents after adjustment for age, sex, education, BMI, smoking and physical activity (24).**

|  |  |  |
| --- | --- | --- |
|  | **OR** | **95% CI** |
|  **World** | 2.36 | 1.91 - 2.92 |
|  **Africa** | 0.86 | 0.54 - 1.37 |
|  **South-America** | 1.98 | 1.46 - 2.68 |
|  **Asia** | 2.16 | 1.38 - 3.37 |
|  **Europe** | 2.47 | 1.73 - 3.52 |

**Table 3: Causes of dementia in people with diabetes**

Alzheimer’s disease 62%

Vascular dementia 17%

Mixed 10%

Lewy body dementia 4%

Parkinson’s disease 2%

Fronto-temporal 2%

Other 3%

**Table 4: Risk factors for Alzheimer’s disease and Vascular dementia**

|  |  |
| --- | --- |
| Alzheimer’s disease | Vascular dementia |
| DyslipidaemiaSmokingHypertensionObesityPhysical inactivityDepressionAlcoholHead injury | DyslipidaemiaSmokingHypertensionObesityAtrial FibrillationPrevious coronary heart disease, stroke of transient ischaemic event |

**Figure 1:**

**Trajectories of cognitive dysfunction in type 1 and type 2 diabetes**

(A) Cognitive dysfunction in patients with type 1 diabetes. Cognitive decrements can be detected soon after onset of diabetes, often in childhood. The width of the shaded area indicates the uncertainty of the estimates, which is larger in older age groups (>65 years for type 1, >80 years for type 2 diabetes) because of the small number of studies. In young adults with type 1 diabetes, cognitive decrements are largest in individuals with an early diabetes onset (black arrow E), and smaller in individuals with a later onset (arrow L). Estimates of the diabetes-associated decrements do not clearly increase with age, consistent with slow progression of the decrements over time. However, some individuals, particularly those with severe microvascular complications (arrow C), might show accelerated decline. (B) In people with type 2 diabetes, estimates of mean cognitive decrements are likewise mostly independent of age. By contrast, the incidence of dementia (blue lines), which is increased in people with diabetes, is strongly dependent on age.

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