Depression and diabetes 2

The link between depression and diabetes: the search for shared mechanisms

Calum D Moulton, John C Pickup, Khalida Ismail

Depression is twice as common in people with type 1 or type 2 diabetes as in the general population, and is associated with poor outcomes. Evidence is growing that depression and type 2 diabetes share biological origins, particularly overactivation of innate immunity leading to a cytokine-mediated inflammatory response, and potentially through dysregulation of the hypothalamic-pituitary-adrenal axis. Throughout the life course, these pathways can lead to insulin resistance, cardiovascular disease, depression, increased risk of type 2 diabetes, and increased mortality. Proinflammatory cytokines might directly affect the brain, causing depressive symptoms. In type 1 diabetes, mediators of depression are not well studied, with research hindered by inconsistent definitions of depression and scarcity of observational, mechanistic, and interventional research along the life course. Despite few studies, evidence suggests that familial relationships and burden of a lifelong disorder with an onset early in personality development might contribute to increased vulnerability to depression. Overall, longitudinal research is needed to identify risk factors and mechanisms for depression in patients with diabetes, particularly early in the life course. Ultimately, improved understanding of shared origins of depression and diabetes could provide the potential to treat and improve outcomes of both disorders simultaneously. These shared origins are targets for primary prevention of type 2 diabetes.

Introduction

An association between depression and diabetes was recognised as early as the 17th century, when British physician Thomas Willis noted that diabetes frequently appeared in individuals who had experienced previous life stresses or sadness. We now know that prevalence of depression in patients with type 1 or type 2 diabetes is about twice that of the general population without diabetes. Both type 1 and type 2 diabetes result in persistent hyperglycaemia, but show important differences in their association with depression, which suggests that the association between each type might be driven by different underlying mechanisms. A bidirectional relation exists between type 2 diabetes and depression, and evidence is growing for biological correlates of depression in patients with type 2 diabetes, but less research into biological mechanisms for depression in patients with type 1 diabetes has been done. The two disorders typically occur at different ages and need different management. Type 1 diabetes presents characteristically in childhood and early adulthood, at a time of rapid psychological and physiological change, whereas type 2 diabetes typically occurs later, in mid-adulthood. Treatment of type 2 diabetes includes diet and lifestyle modification, and oral medication or insulin injections, whereas type 1 diabetes necessitates daily insulin injections or infusions for life. Additionally, average age of onset of depression—early-to-mid-20s—suggests that important differences exist in its relation with type 1 and type 2 diabetes. We therefore discuss type 1 and type 2 diabetes separately in terms of their association with depression.

The gold standard to diagnose depression is a diagnostic interview based on established diagnostic criteria, such as the Schedules of Clinical Assessment in Neuropsychiatry. Much research into both type 1 and type 2 diabetes has instead used self-report questionnaires, sometimes with a cutoff to define depression or to describe depressive symptoms. Results of validation studies in patients with diabetes have shown that self-report questionnaires can substantially overdiagnose clinical depression. However, whether the phenotype of depression in diabetes differs, at least in some patients, from depression in the non-diabetic population is not known. For example, biological symptoms of depression (eg, fatigue, and sleep and appetite disturbance) are often reported in patients with diabetes who do not meet criteria for clinical depression according to a diagnostic interview. We therefore include papers that use both conventional diagnostic criteria and questionnaires to define depression.

The related construct of diabetes-specific distress refers to emotional responses to diabetes, its treatment, and its effects on lifestyle and the future. Although diabetes-specific distress has moderate-to-strong positive correlations with self-report measures of depression, much of the variance in diabetes-specific distress is unexplained. Diabetes-specific emotional distress has been suggested to be a separate psychological construct to depression, and here we regard it as a potential mediator of the association between depression and diabetes self-management.

Type 2 diabetes

Overview

One interpretation for the link between depression and type 2 diabetes is that the psychological burden of life with a chronic disorder predisposes patients to
depression, and depression in patients with type 2 diabetes is associated with poor self-care behaviours. To support this interpretation, risk of depression seems to be higher in people with a diagnosis of type 2 diabetes than in people with impaired glucose metabolism or undiagnosed diabetes. Another explanation is that depression is coincidental with type 2 diabetes because they share similar environmental and lifestyle factors, such as socioeconomic deprivation, social adversity, smoking, and reduced physical activity. For example, childhood adversity (abuse, deprivation, and neglect) has been shown to have effects on depression and self-reported diabetes onset in later life. In adulthood, work stress is associated with increased risk of type 2 diabetes and depression. Additionally, depression typically presents in early adult life and is linked to self-neglect and low self-esteem, which might increase risk of unhealthy lifestyles and, in turn, increase risk of type 2 diabetes. For example, depressive symptoms are associated with high body-mass index (BMI), poor diet, low levels of physical activity, and smoking, all of which are risk factors for type 2 diabetes and cardiovascular disease. The cognitive behavioural model (figure 1) suggests that the burden of type 2 diabetes leads to low mood and negative thoughts about diabetes, which worsen diabetes self-care. Such negative thoughts and behaviours can be identified and modified with cognitive behavioural therapy (CBT) (figure 1), which slightly improves mood and glycaemic control in patients with type 2 diabetes.

Although glycaemic control tends to improve when treatment for depression is integrated with type 2 diabetes management, treatment of depression alone does not consistently improve glycaemic control. Results of cross-sectional studies have shown a modest association between depression and high concentrations of haemoglobin A1c (HbA1c). However, prospective studies—which are few in number—have had mixed results despite the more consistent finding that depression is a strong risk factor for macrovascular complications and dementia in patients with type 2 diabetes. Evidence suggests that diabetes-related distress, rather than depression, is associated with decreased glycaemic control over time. Moreover, the link between depression and type 2 diabetes is bidirectional: type 2 diabetes is associated with a roughly 20% increased risk of incident depression, and depression is associated with a 60% increased risk of incident type 2 diabetes. Collectively, these findings suggest that the relation between depression and type 2 diabetes is complex and that, in some individuals, shared biological mechanisms might underlie the association between, and the course of depression and type 2 diabetes.

Several biological mechanisms have been proposed for the association between diabetes and depression throughout the life course. Depression and diabetes have a moderate genetic correlation of r=0.19 (albeit with a broad CI of 0–0.46), whereas various type 2 diabetes-related single nucleotide polymorphisms have been associated with depression and type 2 diabetes independently. Preliminary evidence suggests that adaptations to the in-utero environment could drive so-called metabolic ageing and predispose patients to depression, potentially via epigenetic mechanisms such as DNA methylation marks. Low birthweight followed by accelerated weight gain in childhood has large effects on incidence of type 2 diabetes in later life, and a meta-analysis showed a statistically significant association between low birthweight and later depression.

Overall, these findings suggest that depression and type 2 diabetes could develop in parallel through shared biological pathways. Key candidate pathways include the innate inflammatory response, the hypothalamic-pituitary-adrenal (HPA) axis, circadian rhythms, and insulin resistance, which all interact with each other. Although physiologically related and not mutually exclusive, we discuss these pathways separately for ease.

**Innate immunity and inflammation**
Activated innate immunity and an acute-phase inflammatory response are implicated in pathogenesis of type 2 diabetes. Specifically, raised concentrations of proinflammatory cytokines lead to pancreatic β-cell apoptosis and insulin resistance, and predict onset of type 2 diabetes in initially non-diabetic patients. The importance of innate immunity in inflammation in type 2 diabetes has been substantiated by systematic reviews of prospective studies. Additionally, anti-inflammatory agents, such as interleukin 1 receptor antagonist and non-steroidal anti-inflammatory drugs, improve glycaemic control in placebo-controlled trials. Growing evidence likewise suggests that the cytokine-mediated inflammatory response is associated with depression in people without diabetes. Increased cytokine serum concentrations activate the HPA axis, increase oxidative stress in the brain, and might activate the tryptophan–kynurenine pathway, resulting in reduced production of serotonin. Depressive symptoms and cognitive deficits are often reported in patients treated with the cytokine interferon αβ. A meta-analysis of the association between cytokines and major depression reported that patients with depression had statistically significantly higher circulating concentrations of tumour necrosis factor (TNF) and interleukin 6 than those without depression. Furthermore, a meta-analysis of four studies reported that adjunctive therapy with the PTGS2 inhibitor celecoxib reduced depressive symptoms. However, participant numbers in these studies were low, and PTGS2 inhibitors are likely to be more problematic in patients with type 2 diabetes because they are associated with increased risk of thrombosis.

Although strong evidence implicates the innate immune system in the pathogenesis of depression in
In a primary-care sample of 1790 patients with newly diagnosed type 2 diabetes, patients with depression—defined by a Patient Health Questionnaire 9 (PHQ-9) score of 10 or more—were more overweight, younger, had higher concentrations of C-reactive protein (CRP) and interleukin 1-receptor antagonist, and higher white-cell counts than people with type 2 diabetes who were not depressed, even after adjustment for key covariates. In other studies, increased concentrations of CRP and interleukin 6 predicted increased risk of type 2 diabetes and depression after adjustment for covariates. A large cohort study of 3573 patients with type 2 diabetes reported a statistically significant cross-sectional association between high CRP concentrations and depression, although after multivariate analysis, this association was shown only in patients with high BMI. In the related specialty of cardiovascular disease, depressive symptoms predict high white-cell counts in patients with stable coronary heart disease, and depression is an independent predictor of cardiovascular mortality after myocardial infarction. Additionally, depression increases risk of incident dementia in patients with type 2 diabetes, with increased concentrations of interleukin 6 associated with cognitive decline in patients with type 2 diabetes.

In epidemiological studies, innate immunity has been proposed as a possible mechanism by which depression and type 2 diabetes could develop as a result of stressors throughout the life course. In cross-sectional research, abuse, neglect, or both before age 16 years are major mediators of the cross-sectional relation between increased concentrations of inflammatory cytokines and depression in adults. Cumulative exposure to low socioeconomic status from childhood to middle age is associated with increased risk of type 2 diabetes in adulthood, with interleukin 6 and CRP acting as independent predictors.

If inflammation is involved in pathogenesis of depression in type 2 diabetes, reduction in inflammation might be a novel treatment. However, no studies have attempted to modify inflammation in treatment of depression in patients with type 2 diabetes. With the potential benefit of improvement of glycaemic control and depressive symptoms concurrently, anti-inflammatory approaches to treatment of depression in patients with type 2 diabetes are awaited.

Figure 1: Cognitive behavioural formulation for the link between depression and type 2 diabetes

A core belief (an absolute statement about diabetes) leads to development of dysfunctional assumptions (rules that guide daily actions and expectations of diabetes management), which in turn leads to problems with management of diabetes. Problem situations in turn lead to negative emotions, physical symptoms, and negative thoughts, which interact with each other, generating a cognitive behavioural cycle. The dashed lines represent two techniques used in cognitive behavioural therapy that aim to break this cycle and thereby improve mood and glycaemic control: cognitive restructuring encourages patients to identify negative thoughts and assess evidence for—and against—them, to generate an objective view; and behavioural experiments are real-life activities done in or between sessions that might help to challenge negative thoughts, such as checking of blood glucose.
The HPA axis

Stress is associated with activation of the HPA axis, which affects glucocorticoid production by the adrenal glands. Chronic stress with associated hypercortisolaemia can lead to increased portal and peripheral free fatty acids. Additionally, hypercortisolaemia impairs the ability of insulin to translocate intracellular SLC2A4 glucose transporters to the cell surface. Chronic hypercortisolaemia can therefore contribute to metabolic syndrome, insulin resistance, and type 2 diabetes.

Some evidence suggests that depression is associated with chronic dysregulation of the HPA axis. Excess cortisol hinders neurogenesis in the hippocampus, a region implicated in both depression and type 2 diabetes. Furthermore, patients with major depression show reduced expression of glucocorticoid-inducible genes TSC22D3 and SGK1, associated with smaller hippocampal volumes. However, studies reporting overactivation of the HPA axis in patients with depression have often focused on inpatients or those with severe or melancholic subtypes, whereas evidence for HPA-axis dysregulation in outpatients—arguably most relevant for controls—has been less convincing.

Nevertheless, the suggested role of HPA-axis dysregulation in both depression and type 2 diabetes provides a plausible common link between the two disorders throughout the life course. In the brain, early stress leads to attenuated development of the hippocampus and amygdala, areas that have a high density of glucocorticoid receptors and persistent postnatal neurogenesis and that are implicated in both depression and type 2 diabetes. Additionally, women with a history of childhood abuse have increased pituitary-adrenal responses to stress compared with controls. However, a study comparing features of the metabolic syndrome in healthy adult controls and adults with depression reported that depression is statistically significantly related with fasting glucose even in the absence of activation of the HPA axis.

If the HPA axis is associated with depression, pharmacological manipulation of the axis could provide novel treatments. Although mineralocorticoid antagonists prevented development of glucocorticoid-induced depressive behaviours in animals, results of clinical studies have not shown improvement in depression with mineralocorticoid agonism or antagonism. Moreover, the tendency for mineralocorticoid antagonists, such as spironolactone, to worsen glycaemic control emphasises the need for clear understanding of any shared aberrations of the HPA axis in depression and type 2 diabetes before pharmacological manipulation of the axis can provide safe and effective new treatments.

Insulin resistance and secretion

A positive association between depression and insulin resistance would increase plausibility of a biological link between depression and type 2 diabetes. A meta-analysis of 21 studies investigating the link between depression and insulin resistance reported a small but statistically significant cross-sectional association, but this link was attenuated in analyses adjusted for bodyweight and other confounders. However, interpretation is limited by a scarcity of longitudinal data in this area; studies included in the meta-analysis used estimates of insulin resistance such as homeostatic model assessment-insulin resistance (HOMA-IR), because the gold standard (the hyperinsulinaemic-euglycaemic clamp) is not practical for large-scale studies. One of the few prospective studies reported that depression was associated with high HOMA-IR values and incident diabetes in middle-aged women, mediated mostly through central adiposity. A 6-year prospective study of adults aged 50–70 years reported that somatic-vegetative symptoms of depression (fatigue, sleep disturbance, and appetite changes) were associated with worsened insulin resistance over time, partly mediated by increased BMI.

If association with depression is clinically significant, reduction of insulin resistance could be a potential treatment for depression, and could slow down development of type 2 diabetes at the same time. Pioglitazone, which reduces insulin resistance by stimulating the nuclear receptor PPARγ and, to a lesser extent, PPARα, has been shown to improve depressive symptoms in patients with bipolar depression, predicted by increased baseline concentrations of interleukin 6, although this trial was uncontrolled. In a double-blind metformin-controlled trial, pioglitazone improved depressive symptoms compared with metformin. Because both drugs increase sensitivity to insulin, no difference in HOMA-measured insulin resistance is expected, but other biological pathways are implicated in this effect. However, because the study was undertaken in a population with polycystic ovarian syndrome, and patients with worsened depressive symptoms (Hamilton Depression Rating Scale >20) were excluded, these results should be treated with caution.

Circadian rhythms

Disruption of normal circadian rhythm is implicated in both depression and type 2 diabetes. Sleep apnoea, which is common in patients with type 2 diabetes, is associated with disruption of circadian rhythm. Extremes of sleep duration have been shown in patients with depression and metabolic syndrome, and increased concentrations of CRP and interleukin 6 have been reported in long sleepers with depression. Patients with depression and patients with type 2 diabetes have common variations in sleep architecture, such as decreased slow-wave sleep and increased rapid eye movement density, associated with increased concentrations of proinflammatory cytokines, such as interleukin 6 and TNF. Such sleep architecture variations can be seen before onset of depressive
after activation by toxins throughout the life course. In patients with type 2 diabetes, clock gene expression has been directly associated with fasting glucose concentrations. In patients with depression, the rapid antidepressant actions of low-dose ketamine and sleep deprivation therapy might be due to resetting of abnormal clock genes and subsequent restoration of circadian rhythms. This finding highlights the translational potential of these emerging biological pathways, and studies investigating the role of clock genes in depression in patients with type 2 diabetes are awaited.

An alternative explanation: antidepressants rather than depression?

Prescription of antidepressant medication, independently of depression itself, has been suggested as a possible link between depression and type 2 diabetes. One study reported that a medication history of more than 200 defined daily doses of conventional antidepressants increased risk of diabetes in patients with moderate or severe depression by 93–165% compared with the general population. However, subsequent analysis by the same authors suggested that the link was not causal. Selective serotonin reuptake inhibitors (SSRIs) improve glucose regulation in the short term in the general population, and use of SSRIs for 1 year in patients with established type 2 diabetes is not associated with reduction of glycaemic control. Because SSRIs are the most frequently prescribed antidepressants with known anorexigenic properties, this finding suggests that they have no causal role in type 2 diabetes. Future research should identify clearly the prospective relation between baseline antidepressant use and development of prediabetes stages, and the extent to which antidepressant use has direct effects on diabetogenic metabolic pathways, rather than being a proxy marker of depression itself.

Summary: depression and type 2 diabetes share biological origins

Despite limitations in methodological quality of many studies, evidence of shared psychological and, increasingly, biological mechanisms for depression and type 2 diabetes is consistent. In some individuals, these shared mechanisms might lead to development of both disorders in parallel. Fetal or maternal stress in utero, cumulative exposure to low socioeconomic status, and poor health behaviours in people with a genetic predisposition might promote dysregulation of the HPA axis, promote disturbance of circadian rhythms, and act as toxins to activate the innate inflammatory response (figure 2). Dysregulation of these biological pathways might lead, in parallel, to insulin resistance and type 2 diabetes, depression, dementia, and cardiovascular disease. Depressive symptoms or depression might arise in patients with diabetes when excess proinflammatory cytokines in the brain lead to increased breakdown of tryptophan to neuroactive metabolites such as kynurenine, and reduced concentrations of serotonin (figure 3). Reasons why depression typically presents at a younger age than type 2 diabetes are not known. Possible hypotheses are that the brain is more sensitive to the end-effects of these biological pathways, or that the effect of environmental stress on the brain is the first event, which, in turn, affects central regulation of metabolism.

Type 1 diabetes

Overview

Patients with type 1 diabetes need a complex management regimen, including regular and frequent monitoring and recording of blood glucose concentrations and calculation and administration of insulin doses in the context of carbohydrate intake and physical activity. People with type 1 diabetes might struggle to accept and adjust to this monitoring to different extents, posing a practical and psychological burden. The cognitive behavioural model is often used to explain the link between depression and type 1 diabetes (figure 4). In type 1 diabetes, CBT has been used to help patients to identify and reframe negative beliefs about their disease, which might otherwise result in overwhelming frustration and abandonment of self-care activities, such as self-monitoring of blood glucose. A systematic review of patients with and without depression identified that psychological treatments, predominantly CBT, slightly
HPA axis dysregulation

Innate immunity and inflammation

Genetic factors
Childhood adversity
Adulthood adversity

Insulin resistance
β-cell apoptosis
Hippocampal atrophy
Endothelial dysfunction
Circadian rhythm disturbance

Dehydration
Type 2 diabetes
Cardiovascular disease
Dementia

In-utero stress and nutrition
Unhealthy lifestyles

Figure 3: Summary of shared biological pathways contributing to pathogenesis of depression and type 2 diabetes throughout the life course
HPA=hypothalamic-pituitary-adrenal.

improved glycaemic control in patients with type 1 diabetes. However, results of an uncontrolled study of group CBT for depression showed reduced depression in the subgroup with type 1 diabetes, but no improvement in glycaemic control.84

In addition to psychological mechanisms, biological mechanisms, such as inflammation and cerebral damage, might have a role in mediation of the link between depression and type 1 diabetes.81 The role of biological pathways might be a barrier to conventional treatments for depression in patients with type 1 diabetes and, conversely, could be a new modifiable target for intervention. However, in a large-scale cohort study of children diagnosed with diabetes before age 20 years, only high concentrations of apolipoprotein B were associated with worsened depressive symptoms in patients with type 1 diabetes after adjustment for confounders.82 Some authors have highlighted parallels in cerebral correlates for depression and type 1 diabetes.83 However, although changes typical of depression, such as hippocampal atrophy, are consistently noted in patients with type 2 diabetes, the cerebral correlates of type 1 diabetes seem to be different, and only thalamic atrophy is a consistent finding.83

Type 1 diabetes is characterised by a much earlier age of onset than type 2 diabetes, and has the potential to cause substantial disruption to normal developmental processes.

Childhood
Depression can be difficult to diagnose in childhood, and few studies have investigated the association between depression and type 1 diabetes during this period. Although some aspects of diabetes management might be done by the children themselves, such as self-administration of insulin, the adult caregiver is mostly responsible for the complex decision making associated with these tasks, such as dosing insulin on the basis of blood glucose readings and diet. Therefore, the relation between depression and type 1 diabetes in childhood take into account both the child and their familial relationships.

Some evidence suggests that children with type 1 diabetes who grow up in an environment of high expressed emotion have poor glycaemic control.84 The burden of parental responsibility during childhood is a prominent theme of qualitative studies in patients with type 1 diabetes.85 In children with type 1 diabetes, evidence suggests that critical parenting behaviours increase depressive symptoms, with associated reduction of self-care behaviours.86 Clinically, addition of structured behavioural group training has been shown to reduce parental stress and, possibly, maintain improved glycaemic control over time.87

Quality of attachment between child and parents or guardians is a plausible mediator of the child’s adjustment to type 1 diabetes and subsequent psychological sequelae. Attachment theory proposes that past experiences with caregivers are incorporated psychologically to form cognitive models that inform future interpersonal relationships, and these patterns of attachment continue into later life.88 Individual differences exist in the way that people regulate their attachment behaviour in response to threats, such as illness. In adults with type 1 diabetes, dismissing attachment style—characterised by low trust of others and excessive self-reliance—is associated with increased risk of poor glycaemic control.89 However, studies examining attachment behaviour, psychological adjustment, and glycaemic control in children with type 1 diabetes are awaited.

Adolescence
The transition from childhood into adolescence necessitates increased independence and diabetes self-management, such as self-monitoring of blood glucose, dietary intake, and insulin dosing.90 behaviours with which depression has been shown to interact adversely.91 This increased independence coincides with emergence of risk-taking behaviours, such as experimentation with tobacco and alcohol, and desire for peer approval. Additionally, onset of puberty results in decreased glucose uptake, owing in part to increased activity of the growth hormone axis.92 In view of these rapid psychological and physiological changes, diabetes-specific distress is well characterised in adolescents with type 1 diabetes, and is associated with poor glycaemic control, prominent negative beliefs about diabetes, and reduced self-efficacy.93 Fear of hypoglycaemia might result in increased anxiety, guilt, and avoidant behaviour.94 Coping skills training in adolescents results in decreased HbA1c concentrations and improved diabetes self-care and quality of life.95 However, a meta-analysis of psychoeducational interventions reported that no programme has proven effective in randomised studies for patients with poor glycaemic control.96

Additionally, type 1 diabetes in adolescence can lead to negative communication and difficulties within the wider family. Family stress is associated with poor glycaemic control in adolescents with type 1 diabetes, and parental stress is a possible mediator of both adolescent depression and poor glycaemic control.

Adolescence is a key period for development of eating disorders, which are likewise associated with depression and the desire for peer approval. Some prospective studies have investigated the association of eating disorders with depression and type 1 diabetes concomitantly, but the interaction is complex. In a case-control study comparing patients with both type 1 diabetes and an eating disorder with those with an eating disorder alone, the group with type 1 diabetes had statistically significantly lower scores on the Beck Depression Inventory—an unexpected outcome. Adolescents with type 1 diabetes and disturbed eating behaviour—a generic term for subthreshold eating disorder symptoms—are far more likely to report depressive symptoms than those with type 1 diabetes alone, but do not consistently have poorer glycaemic control prospectively.

Clinically, if adolescents with depression and type 1 diabetes develop poor diabetes outcomes or have high comorbidity, routine depression screening in patients with type 1 diabetes could improve outcomes. Results of a study of 528 adolescents with type 1 diabetes showed that high scores on the Children’s Depression Inventory (CDI) were associated with decreased blood glucose monitoring frequency and increased HbA1c concentrations. However, in another study, prevalence of depressive symptoms—as measured by the CDI—in patients with poor glycaemic control was similar to prevalence in those with good glycaemic control. These apparently conflicting findings might be due to differences in methods, since correlation between depression score and HbA1c concentration is more sensitive than bivariate comparison of high and low HbA1c concentration in relation to depression score. However, these findings highlight the need for longitudinal assessment of potential benefits of depression screening on type 1 diabetes outcomes, and emphasise the apparent vulnerability of all adolescents, irrespective of HbA1c concentration, to development of depression.

Adulthood

Relative to the many studies of prevalence of depression in patients with type 1 diabetes in adulthood, mechanistic studies of depression have been sparse. A systematic review reported inconclusive evidence that prevalence of depressive symptoms is increased in young adults with type 1 diabetes, but showed that those who are most depressed have poorest glycaemic control. However, cross-sectional evidence suggests that diabetes-specific emotional distress, rather than depression, is associated with poor glycaemic control in adults with type 1 diabetes.
Looking beyond CBT—such as whether attachment theory might help to explain depression in patients with type 1 diabetes.

Future directions

In both type 1 and type 2 diabetes, greater understanding is needed of the similarities and differences between correlates of depressive symptoms, depression, and diabetes-specific distress. In type 1 diabetes, further research is needed to identify risk factors for depression, taking developmental stage into account, by use of systematic models of family dynamics, CBT, attachment theory, and key transition points in adolescence. Further research should investigate potential biological and cerebral correlates of depression in patients with type 1 diabetes, to elucidate potentially modifiable factors for treatment of depression in these patients. In type 2 diabetes, further basic science research, such as studies in animals, could identify clearly the concurrent effects of biological processes, both peripherally and centrally. Although consistent neuroimaging correlates of both type 2 diabetes and depression have been reported separately, almost no studies have investigated the two disorders together. Large, well characterised cohorts are needed to test whether shared origins of depression and type 2 diabetes exist at a genome-wide association significance level. At the same time, future research should examine the longitudinal relation between depression and prediabetes stages, which might provide opportunities for timely interventions to slow down or stop the course of diabetes, depression, or both.

More research is needed to investigate depression and type 2 diabetes concurrently across the life course, and to identify clearly their temporal relation and biological correlates. Because most patients with depression do not develop type 2 diabetes, and vice versa, future research should identify biological characteristics of individuals at high risk of these disorders and associated complications. The further upstream that interventions target these shared biological pathways, the greater the clinical benefit will be. In established type 2 diabetes, for example, identification of biomarkers predicting macrovascular complications could delay or prevent their onset. Characterisation of biomarkers of depression in patients with type 2 diabetes could identify patients who might benefit from anti-inflammatory medications or other immune-modifying therapies. Most excitingly, identification and modification of upstream biomarkers of both depression and type 2 diabetes could, in some cases, wholly prevent development of these two chronic and debilitating disorders.

Contributors

CDM did the literature search and wrote the first draft. KI wrote the outline for the paper. JCP and KI revised the manuscript. All authors approved the final draft.

Declaration of interests

We declare no competing interests.
References
4 Wing JK, Baber T, Brughia T, et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. *Arch Gen Psychiatry* 1990; 47: 589–93.
30 de Mola CL, de França GV, Quevedo LA, Hortá LB. Low birth weight, preterm birth and small for gestational age association with adult depression: systematic review and meta-analysis. *Br J Psychiatry* 2014; 205: 140–47.


54 Frodl T, Carballedo A, Hughes MM, et al. Reduced expression of glucocorticoid-inducible genes GILZ and Sgk-1 high IL-6 levels are associated with reduced hippocampal volumes in major depressive disorder. Transl Psychiatry 2012; 2: e88.


72 Hall MH, Muldoon MF, Jennings JR, Byeuse DJ, Flory JD, Manuck SB. Self-reported sleep duration is associated with the metabolic syndrome in midlife adults. Sleep 2008; 31: 635–43.

73 Kudlow PA, Cha DS, Lam RW, McIntyre RS. Sleep architecture variation: a mediator of metabolic disturbance in individuals with major depressive disorder. Sleep Med 2013; 14: 493–49.


