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REVIEW

Subclinical inflammation and depressive symptoms in patients with type 1 and type 2 diabetes

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Abstract

Depression is a frequent comorbidity of type 1 diabetes (T1D) and type 2 diabetes (T2D). Depression and diabetes are linked by a bidirectional relationship, but the underlying mechanisms are still incompletely understood. Experimental, observational and intervention studies showed that inflammatory processes contribute to the development of depression in animal models and humans. Given the high risk of morbidity and mortality in patients with the double burden of diabetes and depression, this review provides an overview of epidemiological studies that addressed the relationship between biomarkers of inflammation and depressive symptoms or depression in diabetes patients. In patients with T1D, there is some evidence that higher levels of high-sensitivity C-reactive protein (hsCRP), IL-6, IL-1 receptor antagonist (IL-1RA) and sICAM-1 may be related to depressive symptoms or (for hsCRP) lower treatment response. For T2D, hsCRP, IL-1RA, CCL2 and adiponectin or its isoforms were associated with depressive symptoms in at least two studies, whereas positive associations of IL-1β, IL-6 and IL-18 with depressive symptoms or depression were reported from single cohorts. However, the number of studies is too low for any meaningful meta-analysis. Prospective life course studies including both patients with T1D and T2D, a comprehensive assessment of systemic inflammation and repeated assessment of depressive symptoms should represent a future research priority to clarify to what extent subclinical inflammation affects the risk of depression in patients with diabetes. A better understanding of the role of inflammatory processes may help to identify subtypes of depression with partly different pathogenesis, which could have consequences with respect to therapeutic options including immunomodulation.

Keywords Depressive symptoms · Depression · Diabetes · Inflammation · Cytokines

Introduction

Depression is one of the most frequent comorbidities in both patients with type 1 diabetes (T1D) and type 2 diabetes (T2D). The lifetime risk of major depression in the general population has been estimated to reach 16% [1], but for individuals with diabetes, this lifetime risk is approximately twofold higher [2, 3]. Thus, depression must be considered as comorbidity of diabetes in a similar way as cardiovascular disease, neuropathy, chronic kidney disease and retinopathy.

Of note, prospective studies point towards a bidirectional relationship between depression and diabetes [4, 5]. Several potential explanations for this bidirectionality have been proposed. In addition to direct causal effects of diabetes on depression and vice versa, it is conceivable that shared risk factors for both diseases lead to associations in epidemiological studies which may not be causal [6, 7]. Whereas an activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system are mainly discussed as

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mechanisms contributing to the development of depression [6, 8], inflammatory processes are of particular interest in depression research not only because of their relevance in the development of T1D and T2D [6, 9, 10] but also because of their contribution to other diabetic comorbidities. In this context, cardiovascular diseases (CVD) have been studied in detail [11, 12], and recently, the first large RCT demonstrated that the risk of recurrent cardiovascular events can be reduced with an interleukin (IL)-1β inhibitor, i.e. with a purely anti-inflammatory therapy [13]. Prospective studies also indicate that different patterns of immune activation precede the onset of polyneuropathy [14, 15], chronic kidney disease [16–18] and retinopathy [19–21].

Numerous cross-sectional and prospective studies have shown that individuals with depressive symptoms or major depression have higher systemic levels of proinflammatory biomarkers of inflammation [22–25] and that higher levels of biomarkers of inflammation such as high-sensitivity C-reactive protein (hsCRP) and IL-6 are associated with a higher risk to develop depressive symptoms or depression [6, 25, 26]. However, most of these studies were community-based, whereas hardly any data are available for patients with diabetes.

In this review, we will therefore discuss what is known about the relationship between inflammation, diabetes and depression with specific focus on human studies. After an introduction of the clinical relevance of depression as diabetic comorbidity, we will briefly summarise the evidence that inflammation represents a risk factor for depression and give a detailed overview and update on epidemiological studies addressing this question in patients with diabetes. Finally, our conclusions will be linked with a concise discussion of open questions and future research priorities.

Depression and diabetes—clinically relevant comorbidities

The risk for clinical depression as well as subclinical depression is roughly doubled in people with diabetes compared to the general population [27, 28], so that the notion of depression as comorbidity of diabetes is well-established. A meta-analysis of 42 studies demonstrated that 31% of patients with diabetes reported having elevated depressive symptoms compared to 14% among individuals without diabetes. A diagnosis of clinical depression based on standardised criteria as defined by the ICD-10 (10th revision of the International Statistical Classification of Diseases and Health Related Problems) or the DSM-5 (5th edition of the Diagnostic and Statistical Manual of Mental Disorders) was also more frequent among patients with diabetes (11.4%) compared to individuals without diabetes (5.0%) [27]. A newer systematic review yielded similar results of a prevalence between 10% and 20% with clinical depression, depending on the clinical setting [29].

The reason for this high degree of comorbidity of diabetes and depression is unclear. Of note, there is evidence that elevated prevalences of depression are not uncommon in people with chronic diseases. The WHO World Health Survey summarised prevalence rates based on ICD-10 criteria for depression from 60 countries worldwide and found a significantly higher prevalence of depression in people with at least one comorbid somatic complication compared to the healthy general population (3.2%). The prevalence of depression in specific somatic diseases was 9.3% for diabetes mellitus, 15.0% for arthritis, 18.1% for angina pectoris and 18.1% for asthma [30]. A study in the USA yielded similar results [31]. The relative risk for major depression was elevated by 2.6-fold if a somatic disease was present with comorbid depression rates ranging from 7.9% in patients with heart failure to 17% in patients with end-stage renal disease [31]. These data clearly show that the presence of a chronic somatic disease is a risk factor for depression and that the comorbidity of depression and diabetes does not seem to be an exception. However, since the long-term prognosis of diabetes is highly dependent on adequate self-care behaviour, depression most likely has a more clinically relevant impact on the course of diabetes than that of other chronic conditions [32–34].

Given the overall high prevalence of depression in many chronic diseases, it seems reasonable to assume that elevated depression rates are partially explainable by disease-specific distress that contributes to elevated depression scores or even clinical depression in vulnerable individuals [34]. In line with this, a meta-analysis showed that depression was significantly more common in people with treated diabetes than in people with screen-detected diabetes or disturbed glucose tolerance [35]. This may indicate that the experience of having a chronic disease and treatment requirements may have been associated with depression in addition to the metabolic component of glucose intolerance.

However, further studies indicate that depression may also lead to T2D, suggesting a bidirectional relationship between depression and diabetes. As early as in the seventeenth century, Thomas Willis made the observation that prolonged sorrow lead to diabetes [36]. Meta-analyses of prospective studies were able to corroborate this early observation. Two meta-analyses showed identically that the risk to develop T2D is enhanced by 37% in individuals with depression compared to non-depressed individuals at study baseline [37, 38]. The mechanisms linking depression to future diabetes are not fully understood yet. Depression may be associated with less healthy behaviour, sedentary lifestyle and overweight. However, studies which are able to adjust the diabetes risk for lifestyle factors found that such an adjustment attenuated the association between depression and diabetes, but the association between depression and future diabetes remained still

significant [4, 5]. This might indicate the presence of other factors than lifestyle as etiologically important. A meta-analysis on insulin resistance and depression showed that depression was related to insulin resistance, which might be an additional pathway mediating the link between depression and elevated diabetes risk [39]. Immune activation and inflammation could represent a second pathway because adjustment for biomarkers of inflammation (CRP and IL-6) lead to an attenuation of diabetes risk in people with depression [4]. The role of systematic levels of inflammation-related biomarkers for the link between diabetes and depression will be discussed in detail below.

From a clinical perspective, it is important to note that the WHO Health Survey indicated that comorbid depression in combination with other chronic diseases leads to a significantly larger impairment in health than other chronic diseases as comorbidities. This effect was substantially amplified in the case of comorbid depression with diabetes [30]. This is in line with other studies also reporting that the interaction between depression and diabetes resulted in a larger decrease in quality of life than the added effects of depression and diabetes alone [40].

The comorbidity of depression and diabetes has also implications for diabetes self-care behaviour. There is evidence from a meta-analysis that depression might be a barrier for effective diabetes self-care [41]. Patients with diabetes and a higher depression score were characterised by higher rates of non-adherence to oral anti-diabetic medication, less exercise, unhealthier dietary behaviour and less frequent glucose monitoring. More complex self-care behaviours like achieving and maintaining lifestyle changes were more strongly affected by depression than less complex self-care behaviours like adherence to medication [42]. Therefore, it is not surprising that there is an established link between the degree of depression and increasingly poor glycaemic control [42–44].

Depression in people with diabetes is also a risk factor for the occurrence of late complications and functional disabilities. In a prospective study with a 7-year follow-up the hazard ratio (HR) for macrovascular complications was more than three times higher when depressive symptoms were present in patients with diabetes at baseline [45]. For microvascular complications and functional disability, minor depression was a risk factor associated with HRs of 8.6 and 6.9, respectively. The difference between mild and more severe depression with regard to the risk of late complications was surprisingly rather small [45]. Thus, it seems that even milder forms of depression must be taken seriously in clinical practice [46]. In addition to the link with macro- and microvascular complications, mortality is also enhanced in people with the double burden of depression and diabetes with an increase of overall mortality by 46% and a cardiovascular mortality by 39% [47]. The representative National Health and Nutrition Examination Survey (NHANES) revealed a similar elevation of mortality risk in depressed people with diabetes. Mortality was 54% higher in depressed patients compared to non-depressed patients with diabetes [48]. The link with mortality was more pronounced in patients with diabetes and major compared to minor depression [48–50]. Lifestyle factors such as overweight, sedentary lifestyle and smoking were found to partially mediate the relationship between depression and mortality in diabetes, but after adjustment depression was still a significant predictor for mortality in diabetes [50]. This indicates that lifestyle plays an important mediating role between depression and mortality but also points towards additional factors that must be considered to explain the increased mortality rates in patients with depression.

In summary, the empirical evidence demonstrates that the comorbidity of depression and diabetes is clinically relevant because depression impairs quality of life in people with diabetes and also their diabetes self-management. In addition, depression in diabetes is associated with a less favourable prognosis regarding the risk for complications and mortality. The relationship between depression and diabetes is not fully understood. A bidirectional relationship between depression and diabetes is highly probable, since living with the chronic condition of diabetes is a risk factor for depression, but also depression represents a risk factor for future T2D. There is an urgent need to identify and characterise mechanisms and pathways that mediate and explain this relationship because only a better understanding of these links can pave the way to more effective treatment to reduce the excess burden of morbidity and mortality.

Subclinical inflammation and depression—experimental and epidemiological evidence

The aetiology of depression is multifactorial. Psychological, behavioural and social aspects have been discussed above, but it also comprises genetic, metabolic and immunological components [1, 51, 52]. From a pathophysiological perspective underlying mechanisms include the disruption of the interplay between the immune system, metabolism and the central nervous system (CNS) (e.g. altered metabolism of neurotransmitters including serotonin, dopamine and glutamate in the CNS, activation of the HPA axis, activation of the sympathetic nervous system, glucocorticoid resistance, inflammatory processes), but may also involve neurotoxic processes (alterations of neuronal plasticity) and structural changes in different areas of the brain as discussed in more detail in several excellent reviews [6, 10, 51, 53–55]. Here, we focus on the relevance of subclinical inflammation in this context, which may act as mediator between various risk factors and onset of depression [56] or as independent risk factor. Several lines of evidence link inflammatory processes with depression risk: (i)

experimental studies in animal models and humans, (ii) observational studies of community-based or patient cohorts and (iii) intervention studies examining the efficacy of antidepressant treatment [8–10, 52, 53].

First, experimental studies show that immune activation leads to affective symptoms and behavioural changes in rodent models and humans that are indicative of the onset of depressive symptoms [53]. In rodent models, administration of proinflammatory cytokines (e.g. IL-1β, tumour necrosis factor-α (TNFα)) or stimulation of the innate immune system with bacterial lipopolysaccharide (LPS) leads to depression-like behaviour, which can be attenuated by administration of anti-inflammatory cytokines such as IL-10 [53]. In humans, it is known that acute infections are often associated with mood disturbances and depressive symptoms which are adaptive and reversible [10]. Similar effects can be observed when using experimental administration of LPS or following immune activation with vaccines [53, 57] and the onset of depressive symptoms is a common side effect in patients receiving interferon-α (IFNα) or IL-2 as therapy against hepatitis virus infection and cancer, respectively [53].

Of note, the association between inflammation and depression is bidirectional which needs to be considered when interpreting cross-sectional studies. Psychological stressors activate the NF-κB pathway and the Nod-like receptor pyrin containing 3 (NLRP3) inflammasome, resulting in the release of proinflammatory cytokines such as IL-1β, IL-6, IL-18 and TNFα which have been implicated in the risk of depression in experimental and epidemiological studies [58, 59]. Stress-induced alterations are not only limited to immune cells in the periphery, but also affect microglia in the CNS [60].

The second line of evidence comprises data from observational studies with cross-sectional or prospective designs. The most direct assessment of the association between inflammatory processes and the development of depression would involve measurements of an upregulation of proinflammatory biomarkers in the CNS. This is not feasible in epidemiological studies, but it should be noted that a large study using samples from the cerebral cortex of psychiatric patients found direct evidence for a link between inflammation-related gene expression patterns and a dysregulation of the HPA axis in patients with depression [61], which validates the approach to study the link between immune activation and depressive symptoms using systemic biomarkers from peripheral blood. Additionally, a recent study reported that biomarkers of inflammation measured in peripheral blood were highly correlated with biomarkers of inflammation in cerebrospinal fluid, which in turn were linked with depressive symptoms [62]. Peripheral inflammation can reach the CNS via humoral, nervous and chemical pathways, so that a correlation between peripheral and central inflammation is biologically plausible and biomarkers of subclinical inflammation in blood may at least partly reflect central inflammation.

Meta-analyses of cross-sectional studies found that individuals with depressive symptoms or depression have higher levels of several proinflammatory biomarkers than controls without depression with most consistent evidence for the acute-phase protein hsCRP and the cytokine IL-6 [22–25, 63]. Other biomarkers that showed positive associations with the presence of depressive symptoms or depression in several studies include further proinflammatory cytokines (IL-1β, IL-12, IL-18, TNFα); anti-inflammatory cytokines (IL-1 receptor antagonist (IL-1RA), IL-10); soluble forms of cytokine receptors (soluble IL-2 receptor, soluble TNF receptor 2); and chemokines (MCP-1/CCL2 [monocyte chemoattractant protein 1/C-C motif chemokine ligand 2], IL-8/CXCL8 [C-X-C motif chemokine ligand 8]) [22, 24, 63–67]. There appears to be a dose-response relationship between systemic levels of proinflammatory immune mediators and the severity of depression [22, 23], which could argue for a causal relationship. However, the level of adjustment for covariables differs widely between studies, and recent meta-analyses used CRP and IL-6 as examples to demonstrate that confounders such as age, sex, obesity, comorbidities, lifestyle and psychosocial factors and medication use may explain a large part of the raw effect estimated from unadjusted analysis [25, 68]. Therefore, the strength of the association between biomarker levels and depression is still unclear despite the high number of studies in this field. Additionally, as discussed above, there is a bidirectionality in the association between subclinical inflammation and depression, so that studies with a longitudinal design are required to reveal temporal and potentially causal relationships.

Of note, depression is a heterogeneous disease [51] and several studies indicated that biomarkers of inflammation are related to specific symptoms of depression which further complicates the interpretation of study results [8]. Both in the US NHANES and in the English Longitudinal Study of Ageing, higher CRP levels were independently associated with somatic symptoms of depression, but not with cognitive or emotional symptoms [69, 70].

Findings from several prospective studies corroborated these data because higher systemic levels of proinflammatory biomarkers are also associated with a higher risk of incident depressive symptoms or major depression. CRP and IL-6 are the most frequently measured biomarkers in this context, and data for CRP as risk factor of depression are more consistent than for IL-6 [25, 26]. However, risk of confounding, heterogeneity between studies and potential publication bias of both cross-sectional and prospective studies currently limit the informative value of such meta-analyses.

Finally, data from intervention studies provide a third line of evidence that subclinical inflammation and depression are linked in a clinically relevant manner. In a number of studies, biomarkers of inflammation before and after (mostly pharmacological) treatment have been related to treatment response.

Individual studies and meta-analyses showed that antidepressant treatment has the potential to attenuate subclinical inflammation [71–73] and that subsets of patients with higher levels of proinflammatory cytokines, in particular TNFα, may have a less pronounced response to antidepressant treatment compared to patients with lower levels of these cytokines [74, 75]. However, these data were derived from heterogeneous groups of patients and specific data for patients with diabetes are not yet available.

Biomarkers of subclinical inflammation and depression in patients with diabetes

Despite the high proportion of patients with diabetes affected by depressive symptoms or depression, the number of studies addressing the association between biomarkers of inflammation and depression specifically in patients with T1D [76–80] or T2D [76–83] is relatively small. Some of these studies addressed only one diabetes type [81–83], whereas others compared patients with T1D and T2D in the same cohorts [76–80]. Most of these studies were cross-sectional [76, 78, 79, 81–83], while only two studies had a longitudinal or prospective design [77, 80]. Of note, all studies adjusted for multiple confounders to reduce the risk of bias.

Table 1 provides an overview of studies on biomarkers of inflammation and depression in patients with T1D. In the SEARCH for Diabetes in Youth Study comprising children and adolescents with T1D, higher CRP was associated with depression, but this association was not significant in the adjusted model [76]. Higher levels of IL-6 and soluble intercellular adhesion molecule 1 (sICAM-1) were associated with depressive symptoms in adult patients with recent-onset T1D from the German Diabetes Study, but the association for IL-6 was attenuated by adjustment for confounders [78]. The analysis of baseline data from two intervention studies in T1D patients with longer disease duration aiming at reducing diabetes distress and depressive symptoms showed that higher levels of hsCRP and IL-1RA were associated with depressive symptoms after full adjustment [79]. However, when these patients were followed up for 12 months, changes in neither biomarker nor in any of the others included in the study (IL-6, IL-18, CCL2, adiponectin) were linked to reductions in depressive symptoms, and baseline biomarker levels were also not related to treatment response [80]. In contrast, higher hsCRP levels were linked to less pronounced reduction of depressive symptoms in the Diabetes and Depression study in which adults patients with T1D were randomised to diabetes-specific group cognitive behavioural therapy or sertraline treatment and followed-up for 15 months [77]. Taken together, there is preliminary evidence that higher levels of hsCRP, IL-6, IL-1RA and sICAM-1 may be related to depressive symptoms or (for hsCRP) lower treatment response, but overall not enough studies are available and data are too inconsistent to draw any sound conclusions for T1D.

Table 2 summarises the available data for associations between biomarkers of inflammation and depressive symptoms or depression in patients with T2D. While no association between biomarkers and depression were found in the SEARCH for Diabetes in Youth Study [76], higher IL-6 levels were linked with depression in a small group of participants from the Health, Ageing and Body Composition study [81]. Higher hsCRP was related to major depression in the Diabetes Distress and Care Registry at Tenri in the age- and sex-adjusted analysis, but not upon further adjustment [82]. A large panel of 11 biomarkers of inflammation were investigated in the South London Diabetes Study, which found positive associations of hsCRP, IL-1β, IL-1RA, CCL2 and white blood cell count with depressive symptoms in the fully adjusted model [83]. In the German Diabetes Study, higher hsCRP and a higher ratio of high molecular weight (HMW)/total adiponectin was associated with depressive symptoms [78] in patients with recent-onset T2D, whereas higher hsCRP, IL-18 and IL-1RA as well as lower adiponectin levels were found associated with depressive symptoms in patients with a longer duration of T2D [79]. In the latter study cohort, reductions in depressive symptoms over 12 months were related to reductions in hsCRP, IL-18 and IL-1RA and higher baseline CCL2 levels were associated with lower treatment response [80]. The second longitudinal study included only hsCRP and found no link between baseline levels and changes in depressive symptoms [77]. In summary, hsCRP, IL-1RA, CCL2 and adiponectin or its isoforms were associated with depressive symptoms in at least two study samples, whereas positive associations of IL-1β, IL-6 and IL-18 with depressive symptoms or depression were reported from single cohorts. Although there are more studies on associations between inflammation and depression for T2D compared to T1D, the number of studies is too low to explain the heterogeneity of findings and precludes any meaningful meta-analysis. Overall, the cumulative evidence is still weak, and positive findings from the aforementioned studies need further replication.

In the context of T2D, data from population-based studies are also of interest, if they consider the impact of diabetes type in stratified analyses or by testing interactions by diabetes type. The Maastricht Study is a population-based study with an oversampling of individuals with T2D. In a study sample in which 29% of all participants had a diagnosis of T2D, a sum score for low-grade inflammation containing CRP, TNFα, serum amyloid A (SAA), sICAM, IL-6 and IL-8/CXCL8 was positively associated with depressive symptoms and depressive disorder without significant interaction by diabetes status, indicating that associations did not differ between individuals without and with T2D [84].

Table 1 Overview of studies assessing the relationship between systemic biomarkers of inflammation and depressive symptoms or depression in individuals with T1D

Study population and design	Depression outcome	Biomarkers of inflammation	Main findings	Reference
SEARCH for Diabetes in Youth (SEARCH; USA) - 2007 children with T1D < 20 years - Population-based - Cross-sectional	CES-D score (CES-D categories 0–15, 16–23, ≥ 24)	CRP, IL-6, SAA, adiponectin, leptin	Differences between categories for CRP ($P < 0.006$; highest CRP for CES-D ≥ 24) in the unadjusted analysis, but no difference after adjustment for age, sex, BMI, duration of diabetes, HbA1c, race/ethnicity, highest parental education, health insurance coverage, number of caregivers in the home	[76]
Diabetes and Depression (DAD) study (Germany) - 106 adult patients with T1D randomised to 12-week diabetes-specific group CBT or sertraline treatment - Hospital-based - Intervention study - Follow-up 15 months	Change in the HAMD-17 score	hsCRP	Higher baseline hsCRP associated with less improvement of HAMD-17 over follow-up of 12 weeks ($\beta = -0.276$, $P = 0.009$) and 15 months ($\beta = -0.282$, $P = 0.006$) (adjusted for age, sex, BMI, baseline HbA1c, baseline HAMD-17, treatment group)	[77]
German Diabetes Study (Germany) - 139 adults patients with recent-onset T2D - Community-based - Cross-sectional	CES-D	hsCRP, IL-6, IL-18, total adiponectin, HMW adiponectin, sICAM-1, sE-selectin	- Higher IL-6 and higher sICAM-1 associated with higher CES-D score ($P < 0.05$; adjusted for age, sex, BMI) - Higher sICAM-1 associated with higher CES-D score ($P < 0.05$) in the full model (adjusted for age, sex, BMI, HbA1c, HDL cholesterol, LDL cholesterol, triglycerides, hypertension, lipid-lowering medication, use of NSAIDs, number of diabetes-related comorbidities - Associations not significant after Bonferroni correction for multiple testing	[78]
Bad Mergentheim (Germany) - 389 adult patients with T2D - Hospital-based - Cross-sectional	CES-D, PHQ-9, WHO-5	hsCRP, IL-6, IL-18, IL-1RA, CCL2, adiponectin	IL-1RA positively associated with two depression scores (CES-D, PHQ-9) and hsCRP positively associated with depressive symptoms for one score (WHO-5) after adjustment for age, sex, study, BMI, HbA1c, time since diagnosis of diabetes, total cholesterol, triglycerides, use of lipid-lowering drugs, hypertension, use of NSAIDs, use of antithrombotic medication, use of antidepressant medication, number of diabetes-related comorbidities ($P < 0.05$)	[79]
Bad Mergentheim (Germany) - 167 adult patients with T2D - Hospital-based intervention study - Follow-up 12 months	Change in CES-D over 12 months	hsCRP, IL-6, IL-18, IL-1RA, CCL2, adiponectin	No associations between reductions in CES-D and changes in biomarkers, no associations of baseline biomarker levels with reduction in CES-D score; all analyses adjusted for biomarker levels at baseline, age, sex, study cohort, diabetes duration, HbA1c, number of diabetes-related comorbidities, BMI, cholesterol, triglycerides, lipid-lowering medication, hypertension, NSAIDs, anti-thrombotic medication	[80]

BMI body mass index, *CBT* cognitive behavioural therapy, *CCL* C–C motif chemokine ligand, *CES-D* Center for Epidemiologic Studies Depression, *CRP* C-reactive protein, *HAMD-17* Hamilton Depression Rating Scale, *HDL* high-density lipoprotein, *HMW* high molecular weight, *hsCRP* high-sensitivity C-reactive protein, *IL* interleukin, *IL-1RA* interleukin-1 receptor antagonist, *LDL* low-density lipoprotein, *NSAID* non-steroidal anti-inflammatory drugs, *PHQ-9* Patient Health Questionnaire-9, *SAA* serum amyloid A, *sE-selectin* soluble E-selectin, *sICAM-1* soluble intercellular adhesion molecule-1, *TNF* tumour necrosis factor, *T1D* type 1 diabetes, *WHO-5* 5-item World Health Organisation Well-Being Index

Table 2 Overview of studies assessing the relationship between systemic biomarkers of inflammation and depressive symptoms or depression in individuals with T2D

Study population and design	Depression outcome	Biomarkers of inflammation	Main findings	Reference
SEARCH for Diabetes in Youth (USA) - 333 children with T2D <20 yrs. - Population-based - Cross-sectional	CES-D score (categories CES-D 0–15, 16–23, ≥ 24)	CRP, IL-6, SAA, adiponectin, leptin	No differences between depression categories in the unadjusted analysis and after adjustment for age, sex, BMI, duration of diabetes, HbA1c, race/ethnicity, highest parental education, health insurance coverage, number of caregivers in the home	[76]
Health, Ageing, and Body Composition study (USA) - 628 adult patients with T2D only, 14 patients with T2D and depression - Medicare-based - Cross-sectional	Elevated depressive symptoms based on CES-D ≥ 20	CRP, IL-6, TNFα	Higher IL-6 levels in group with T2D and depressive symptoms compared to T2D only (adjusted for age, race, gender, study site, percent body fat, smoking status, statin use, acute respiratory infections, heart and lung disease)	[81]
Diabetes Distress and Care Registry at Tenri (DDCRT) (Japan) - Based on diabetes registry - 3573 adult patients with T2D (including 122 with major depression) - Cross-sectional	Major depression (diagnosis based on PHQ-9)	hsCRP	Positive association between hsCRP and major depression in age- and sex-adjusted analysis (OR (95% CI) 1.86 (1.01; 3.42)) for highest CRP quintile (with third quintile as reference), but no significant association after further adjustment for smoking, type of diabetes therapy, diabetic nephropathy, arthritis, use of NSAID, exercise	[82]
South London Diabetes study (UK) - 1227 adult patients with T2D - Population-based - Cross-sectional	PHQ-9	hsCRP, IL-4, IL-6, IL-10, VEGF, TNFα, IL-1β, IL-1RA, MCP-1/CCL2, WBC, adiponectin	- Positive associations of hsCRP, VEGF, IL-1β, IL-1RA, MCP-1/CCL2 and WBC (r between 0.07 and 0.16, $P < 0.05$) and negative association of adiponectin ($r = -0.07$, $P < 0.05$) with PHQ-9 score in the unadjusted analysis - Positive associations of hsCRP, IL-1β, IL-1RA, MCP-1/CCL2, and WBC ($P < 0.05$) with PHQ-9 score after adjustment for age, sex, ethnicity, BMI, HbA1c, smoking, history of macrovascular disease and prescribed medications	[83]
Diabetes and Depression (DAD) study (Germany) - 113 adult patients with T2D randomised to 12-week diabetes-specific group CBT or sertraline treatment - Intervention study - Hospital-based - Follow-up 15 months	Change in the HAMD-17 score	hsCRP	No association between baseline hsCRP and improvement of HAMD-17 over follow-up of 12 weeks and 15 months (adjusted for age, sex, BMI, baseline HbA1c, baseline HMAD-17, treatment group)	[77]
German Diabetes Study (Germany) - 295 adults patients with recent-onset T2D - Community-based - Cross-sectional	CES-D	hsCRP, IL-6, IL-18, total adiponectin, HMW adiponectin, sICAM-1, sE-selectin	- Higher hsCRP and higher ratio HMW/total adiponectin associated with higher CES-D score ($P < 0.05$), adjusted for age, sex, BMI, HbA1c, HDL cholesterol, LDL cholesterol, triglycerides, hypertension, lipid-lowering medication, use of NSAIDs, number of diabetes-related comorbidities. - Association between ratio HMW/total adiponectin and CES-D significantly associated after Bonferroni correction for multiple testing	[78]
Bad Mergentheim (Germany) - 204 adult patients with T1D - Hospital-based - Cross-sectional	CES-D, PHQ-9, WHO-5	hsCRP, IL-6, IL-18, IL-1RA, CCL2, adiponectin	IL-18 and IL-1RA positively associated with depressive symptoms for two scores (IL-18: PHQ-9, WHO-5; IL-1RA: CES-D, WHO-5), hsCRP positively associated with one depression score (PHQ-9), adiponectin inversely associated with one depression score (PHQ-9) after adjustment for age, sex, study, BMI, HbA1c, time since diagnosis of diabetes, total cholesterol, triglycerides,	[79]

Table 2 (continued)

Study population and design	Depression outcome	Biomarkers of inflammation	Main findings	Reference
			use of lipid-lowering drugs, hypertension, use of NSAIDs, use of antithrombotic medication, use of antidepressant medication, number of diabetes-related comorbidities ($P < 0.05$)	
Bad Mergentheim (Germany) - 103 adult patients with T1D - Hospital-based intervention study - Follow-up 12 months	Change in CES-D over 12 months	hsCRP, IL-6, IL-18, IL-1RA, CCL2, adiponectin	Reductions in CES-D associated with reductions in hsCRP, IL-18 and IL-1RA ($P \leq 0.016$), higher CCL2 at baseline associated with lower reduction in CES-D score ($P = 0.018$); all analyses adjusted for biomarker levels at baseline, age, sex, study cohort, diabetes duration, HbA1c, number of diabetes-related comorbidities, BMI, cholesterol, triglycerides, lipid-lowering medication, hypertension, NSAIDs and anti-thrombotic medication	[80]

BMI body mass index, *CBT* cognitive behavioural therapy, *CCL* C–C motif chemokine ligand, *CES-D* Center for Epidemiologic Studies Depression, *CI* confidence interval, *CRP* C-reactive protein, *HAMD-17* Hamilton Depression Rating Scale, *HDL* high-density lipoprotein, *HMW* high molecular weight, *hsCRP* high-sensitivity C-reactive protein, *IL* interleukin, *IL-1RA* interleukin-1 receptor antagonist, *LDL* low-density lipoprotein, *MCP*, monocyte chemoattractant protein, *NSAID* non-steroidal anti-inflammatory drugs, *OR* odds ratio, *PHQ-9* Patient Health Questionnaire-9, *SAA* serum amyloid A, *sE-selectin* soluble E-selectin, *sICAM-1* soluble intercellular adhesion molecule-1, *TNF* tumour necrosis factor, *T2D* type 2 diabetes, *VEGF* vascular endothelial growth factor, *WBC* white blood cell count, *WHO-5* 5-item World Health Organisation Well-Being Index

Given the data from study cohorts with T1D and T2D, it is not possible to conclude if associations between biomarkers of inflammation and depressive symptoms differ between community or population-based studies and patients with diabetes. There appears a large overlap of depression-related biomarkers of inflammation between both types of study samples pointing towards an upregulation of acute-phase proteins, pro-inflammatory cytokines, chemokines and markers of vascular inflammation in patients with depressive symptoms or depression. With respect to anti-inflammatory biomarkers, systemic levels of IL-1RA have been found positively associated with depressive symptoms and depression in individuals without and with diabetes, which may appear counterintuitive. However, this finding is in line with other observations that higher IL-1RA levels are associated with higher risk of T2D, cardiovascular disease and other diabetic comorbidities [14, 85, 86]. Higher IL-1RA levels in individuals at higher cardiometabolic risk may reflect IL-1β-related processes (IL-1β can induce IL-1RA as endogenous inhibitor) or may be caused by other proinflammatory and/or metabolic stimuli that increase cardiometabolic risk [86].

It is interesting that the few studies comprising both patients with T1D and T2D found differences in the associations between biomarkers of inflammation and depressive symptoms. Some studies found more evidence for associations between biomarkers of inflammation and depressive symptoms in T2D compared with T1D [78–80], whereas one study identified associations between hsCRP and treatment response in T1D only [77]. Such differences may be related to differences in the inflammatory contribution to T1D vs T2D [52] and are in line with other recent data pointing towards differences in the associations of inflammation with diabetic comorbidities between both diabetes types for other diabetic complications including DSPN and cardiovascular autonomic neuropathy [87–89].

Conclusions and outlook

The contribution of inflammatory processes to the development of depressive symptoms has been clearly demonstrated by experimental studies using animal models, clinical studies involving the administration of proinflammatory cytokines, epidemiological studies linking biomarkers of inflammation with depression and finally, treatment studies pointing towards an interaction between inflammatory status and treatment response [53]. However, most of these studies did not consider the potential relevance of diabetes for the relationship between subclinical inflammation and depression. Subclinical inflammation is most likely important as shared biological pathway predisposing to both diabetes and depression, but also represents a modifiable risk factor for the development

of depression and other comorbidities in patients with diabetes.

Although subclinical inflammation has been implicated as an important pathomechanism in patients with the double burden of diabetes and depression [6, 52], this issue remains largely unexplored because of the scarcity of relevant studies. Additionally, the majority of studies in patients with diabetes have a cross-sectional design, allowing only correlational analyses of the association between biomarkers of inflammation and depression status. This is an important limitation given the bidirectional association between inflammation and depression and because of higher risk for residual confounding. Even longitudinal studies are based on usually only two examinations (baseline and one follow-up) and thus represent random snapshots, whereas the complexity of onset and remission of depression would require a life course approach with multiple assessments of risk factors and outcomes. With respect to outcomes, more clarity and precision in the terminology with respect to depressive symptoms, depressive disorders as psychiatric diagnosis and diabetes distress would help to better compare results from different studies.

From the mechanistic perspective, it is important to note that even studies in community- and population-based samples are often are limited to few biomarkers of inflammation. Reliable evidence for associations between subclinical inflammation and depression from meta-analyses is only available for hsCRP and IL-6 [22–25], which do not reflect the complexity of potentially relevant immunological mechanisms. Moreover, only few studies considered the impact of diabetes type [76–80], although the underlying pathomechanisms leading not only to T1D and T2D in the first place, but also to later comorbidities and complications may at least in part differ [90, 91]. Thus, prospective life course studies including both patients with T1D and T2D, a comprehensive assessment of systemic inflammation and repeated assessment of depressive symptoms should represent a research priority in order to address the question to what extent subclinical inflammation affects the risk of depression in patients with diabetes and if findings are specific for or shared between both diabetes types [51].

The clinical benefit of further studies in this field could comprise more individualised treatment strategies. A better understanding of the role of subclinical inflammation may help to identify subtypes of depression with partly different pathogenesis, which would have consequences with respect to therapeutic options, if different modifiable risk factors or pharmacological targets could be validated (e.g. immunomodulation for subgroups of patients) [8, 73]. This could in particular help people with treatment-resistant depression [66]. It has been hypothesised that immunomodulation may help to target upstream mechanisms in the aetiology of depression rather than downstream effects such as changed neurotransmitter levels, which holds promise for disease modification rather than treatment of symptoms [93]. In order to estimate the clinical relevance of immunomodulation, randomised clinical trials using anti-inflammatory treatment, most likely in combination with cognitive-behavioural therapy and/or antidepressants, will be another research priority. One challenge for such approaches consists in defining immunomodulating treatments (i.e. type of immunomodulating agent, dosage, timing of treatment) that are effective to prevent/treat depressive symptoms but do not compromise immune defence mechanisms [10]. It is conceivable that immunomodulation may even have adverse effects in patients without increased inflammation, so that the interaction of anti-inflammatory therapy as add-on to an antidepressant with baseline inflammation (e.g. hsCRP levels > 3 mg/l) is currently being investigated in randomised controlled trials [94]. Since patients with diabetes and depression are at higher risk of other microvacular and macrovascular complications, effective forms of immunomodulation may also address several public health burdens simultaneously and help to reduce overall morbidity and mortality. Of note, most environmental risk factors for T2D, depression and other comorbidities (e.g. diet, obesity, physical inactivity, psychosocial stress, early life adversity) are proinflammatory, but the potential health benefits of lifestyle-based immunomodulation still appears underappreciated [56, 95].

Regarding further research challenges and priorities, the improvement of neuroimaging methods to assess preexisting inflammation and potential effects of novel treatment approaches on inflammation and brain activity with respect to depression would be timely and valuable. While genetic studies so far did not provide evidence that inflammatory processes are involved in the aetiology of depression [95], it remains possible and biologically plausible that a range of environmental and behavioural factors affect epigenetic processes. Long-lasting epigenetic alterations can permanently modify gene expression patterns and thus influence subclinical inflammation and risk of depression.

In conclusion, subclinical inflammation and depressive symptoms appear tightly interrelated. Depression is a common comorbidity of diabetes, but epidemiological studies addressing the relationship between subclinical inflammation and depression specifically in patients with diabetes are scarce. There is preliminary evidence that inflammation-related biomarkers are associated with depressive symptoms in patients with diabetes in cross-sectional and longitudinal studies. Assessment of subclinical inflammation may help to identify subtypes of depression, and immunomodulating treatment could support cognitive behavioural therapy and antidepressant treatment in particular in patients who respond poorly to current treatment options. Immunomodulation may also hold promise for the prevention of further diabetic comorbidities that characterise the poor prognosis of patients with the double burden of diabetes and depression.

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Compliance with ethical standards

Conflicts of interests The authors declare that they have no conflicts of interest.

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