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## Longitudinal associations between biomarkers of inflammation and changes in depressive symptoms in patients with type 1 and type 2 diabetes

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## ABSTRACT

**Background:** Depressive disorders represent a frequent comorbidity of type 1 diabetes (T1D) and type 2 diabetes (T2D). Subclinical inflammation increases the risk of depressive symptoms in the general population, but the relationship appears complex and bidirectional, and longitudinal data from patients with diabetes are lacking. Therefore, this study aimed to analyse associations between changes in depressive symptoms and changes in biomarkers of inflammation in patients with T1D and T2D and to investigate the hypothesis that higher baseline levels of biomarkers of inflammation are related to a less pronounced reduction of depressive symptoms over time.

**Methods:** Depressive symptoms and systemic levels of six biomarkers of inflammation were assessed in 168 individuals with T1D and 103 individuals with T2D who participated in baseline and 1-year follow-up examinations. Data were obtained from two matching randomised controlled trials addressing diabetes distress and depressive symptoms. Longitudinal associations between biomarkers and depressive symptoms were estimated using linear regression models adjusting for multiple confounders.

**Results:** In patients with T2D, reductions in depressive symptoms were associated with reductions in high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-18 and IL-1 receptor antagonist (IL-1RA) ( $P \leq 0.016$ ), whereas no associations were seen for IL-6, CCL2 and adiponectin. Higher CCL2 levels at baseline were associated with lower subsequent reduction in depressive symptoms ( $P = 0.018$ ). Neither baseline levels nor changes in biomarkers in subclinical inflammation were associated with changes in depressive symptoms in patients with T1D.

**Conclusions:** Reductions of depressive symptoms were longitudinally associated with reductions in biomarkers of inflammation in patients with T2D. Higher baseline CCL2 levels were related with lower reduction of depressive symptoms in this group. No such associations were observed in patients with T1D, suggesting that risk factors and pathomechanisms linking inflammation and depression may differ between diabetes types.

### 1. Introduction

Prospective studies demonstrated that higher circulating levels of inflammation-related biomarkers are associated with the development of depressive disorders (Valkanova et al., 2013). This concept has been corroborated by mechanistic studies (Korzak et al., 2011; Stuart and Baune, 2012; Moulton et al., 2015; Miller and Raison, 2016). However,

these data were predominantly derived from population or community-based studies (Milaneschi et al., 2009; Gimeno et al., 2009; Valkanova et al., 2013), whereas data regarding the relationship between inflammation and depressive symptoms or depression for patients with diabetes are mostly limited to cross-sectional studies (Hood et al., 2012; Doyle et al., 2013; Laake et al., 2014; Hayashino et al., 2014; Herder et al., 2017b, 2018). This is an important gap in the literature because

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(i) depression constitutes a common comorbidity of diabetes (Nouwen et al., 2010; Buchberger et al., 2010; Korczak et al., 2011; Meurs et al., 2016), (ii) both diabetes and depression may have inflammatory processes as underlying common causes (Korczak et al., 2011; Tabak et al., 2014; Moulton et al., 2015) and (iii) the double burden of both conditions increases the challenge of providing optimal care to affected persons (Pouwer, 2017).

The relationship between inflammation and depression is most likely bidirectional. On the one hand, there is evidence that the experimental induction of depressive symptoms leads to an activation of the innate immune system involving inflammasomes and cytokines of the interleukin (IL)-1 family (Prossin et al., 2016). Furthermore, a reduction of depressive symptoms was found to be associated with lower levels of biomarkers such as IL-6 and C-reactive protein (CRP) (Hannestad et al., 2011; Hiles et al., 2012b). On the other hand, higher baseline levels of inflammation precede the onset of depressive symptoms (Valkanova et al., 2013) and may be associated with lower response to anti-depressive treatments (Strawbridge et al., 2015; Baumeister et al., 2016). Again, comparable data on the longitudinal and bidirectional relationship for patients with diabetes are lacking.

Therefore, this study assesses the bidirectional relationship between inflammation and depressive symptoms in patients with type 1 diabetes (T1D) and type 2 diabetes (T2D) using longitudinal data from two randomised controlled clinical trials (RCTs) for diabetes distress and depressive symptoms. Regardless of the treatment allocation this post hoc analysis aims (i) to analyse associations between the reduction of depressive symptoms and changes in biomarkers of inflammation during the 1-year follow-up period, and (ii) to investigate the hypothesis that higher baseline levels of biomarkers of inflammation are related to less pronounced reductions in depressive symptoms during the follow-up period.

## 2. Study population and methods

### 2.1. Study population and design

This study combined longitudinal data from two related RCTs with comparable study samples and treatment procedures. The trials were conducted monocentrically at the Diabetes Centre Mergentheim, an inpatient diabetes centre in Germany, and investigated effects of cognitive-behavioural therapy on elevated depressive symptoms and diabetes distress in patients with T1D and T2D with follow-up assessments after 12 months (ClinicalTrials.gov Identifiers NCT01009138 and NCT01812291). The studies were approved by the Ethics Committee of the State Medical Chamber of Baden-Württemberg, Germany (file numbers 2009-034-f and F-2013-011) and were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent.

The first study assessed the efficacy of a diabetes-specific cognitive-behavioural group treatment programme ('DIAMOS' [for Strengthening Diabetes Motivation]) to reduce depressive symptoms by addressing diabetes-related distress as well as diabetes-independent stressors (Hermanns et al., 2015; Schmitt et al., 2017). Inclusion criteria were diabetes, elevated depressive symptoms (Center for Epidemiologic Studies Depression [CES-D] score)  $\geq 16$ , age 18–70 years and sufficient German language skills. Patients were not eligible if they had severe major depression, schizophrenia/psychotic disorder, severe eating disorder, bipolar disorder, addictive disorder or personality disorder, reported current psychotherapeutic or psychiatric treatment or antidepressive medication or if they were bedridden or under guardianship. Treated participants received five two-hour sessions of group-based diabetes-specific cognitive behavioural therapy (CBT) using the DIAMOS program and four booster calls during the follow-up period. The patients in the control group participated in a standard group-based diabetes education programme with four control calls during the follow-up period; this was also found to be associated with a

subsequent reduction in depressive symptoms (Hermanns et al., 2015).

The second study built upon the first one and incorporated the DIAMOS group programme into a cognitive-behavioural stepped care approach for comorbid depression and diabetes distress in patients with diabetes (acronym: ECCE HOMO). Inclusion and exclusion criteria for the ECCE HOMO study were similar to those of the DIAMOS study with the exception that persons with either elevated depressive symptoms (CES-D score  $\geq 16$ ) or elevated diabetes-related distress (Problem Areas in Diabetes Questionnaire [PAID]  $> 40$ ) could be included. All participants in the intervention group received the DIAMOS group treatment (see above) as first step; in case of insufficient depressive symptom reduction (i.e. less than 50% decrease of the depression score), a telephone-supported bibliotherapy was offered (second step); in case of still insufficient symptom reduction, patients were advised to initiate standard outpatient therapy for depression (third step). Since only 31% and 11% of the treated persons received the second and third treatment steps, respectively, treatment procedures were mostly similar to those in the first study, enabling aggregation of the data for our present analysis. Participants in the control group, as in the DIAMOS study, received standard diabetes education and four control calls during the follow-up period.

Fig. A1 presents an overview of the study design combining both trials. Baseline data were available for 290 individuals with T1D and 154 individuals with T2D. We had to exclude 122 individuals with T1D and 51 individuals with T2D because of loss to follow-up or because no blood samples for immunological analyses were available from the follow-up time-point. This left an analysis sample of 168 individuals with T1D and 103 individuals with T2D.

### 2.2. Assessment of depressive symptoms

A psychiatric interview (Composite International Diagnostic Interview/CIDI; Andrews and Peters, 1998) was performed to exclude patients with severe comorbid mental diseases, bipolar depressive disorders and major depression with suicidal ideation. Depressive symptoms were assessed using the German version of the CES-D questionnaire (Hautzinger, 1988; Hautzinger et al., 2012) to be filled in by the participants. The CES-D detects depressive symptoms within the previous week and can be used for the longitudinal monitoring of depressive symptoms in individual patients (Radloff, 1997; Vilagut et al., 2016). Patients received the questionnaire from an experienced clinical psychologist with precise instructions and the opportunity to clarify any questions. The CES-D score ranges from 0 to 60 points with a higher score indicating higher depressive symptoms. For our analyses we (i) applied the continuous scores to make optimal use of the inter- and intra-individual variations in depressive symptoms and (ii) created a dichotomous criterion for a clinically relevant reduction of depressive symptoms, i.e. decrease of the CES-D score by 50% or more versus a smaller decrease or even increase of the score.

### 2.3. Quantification of biomarkers of inflammation

Biomarkers of inflammation were measured in fasting serum samples obtained between 06:30 a.m. and 08:00 a.m. The same assays and control sera were used for samples from both study populations. Baseline and follow-up samples from patients were always assessed on the same plate to reduce measurement imprecision. Serum high-sensitivity CRP (hsCRP) was measured using an immunoturbidimetric assay, IL-6, IL-1 receptor antagonist (IL-1RA), IL-18, CC-chemokine ligand 2 (CCL2, also known as monocyte chemoattractant protein-1/MCP-1) and total adiponectin were quantified using commercially available ELISA kits as reported before (Herder et al., 2018).

### 2.4. Data collection for confounding variables

Demographic, anthropometric and clinical data were collected using

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