Brain, Behavior, and Immunity 61 (2017) 137–145

Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full-length Article

Associations between inflammation-related biomarkers and depressive symptoms in individuals with recently diagnosed type 1 and type 2 diabetes

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ARTICLE INFO

Article history:
Received 1 September 2016
Received in revised form 28 December 2016
Accepted 28 December 2016
Available online 29 December 2016

Keywords:
Inflammation
Biomarkers
Type 1 diabetes
Type 2 diabetes
Depression

ABSTRACT

Depressive disorders represent a frequent comorbidity of both type 1 (T1D) and type 2 diabetes (T2D). Inflammation-related processes have been implicated in the development of both diabetes and depression. This study aimed to investigate whether biomarkers of subclinical inflammation were associated with depressive symptoms in individuals with recently diagnosed diabetes and if such associations differed by diabetes type.

This cross-sectional study was based on 295 individuals with T2D (67% men, mean age 53 years) and 139 individuals with T1D (60% men, mean age 36 years) of the German Diabetes Study. The main inclusion criterion was a known disease duration of <1 year. Depressive symptoms were assessed with the Allgemeine Depressionsskala, Langversion (ADS-L) questionnaire, the German version of the Center for Epidemiological Studies Depression scale (CES-D) questionnaire. Associations between biomarkers of subclinical inflammation and the ADS-L as continuous score were assessed using multiple linear regression models adjusting for age, sex, body mass index, HbA1c, lipids, hypertension, medication and comorbidities.

Serum high-sensitivity C-reactive protein (hsCRP) and the ratio of high-molecular-weight (HMW)/total adiponectin were positively associated with ADS-L in T2D (both $P < 0.01$), but not in T1D. In contrast, serum levels of soluble intercellular adhesion molecule (sICAM)-1 were positively associated with ADS-L only in T1D ($P = 0.035$). The latter association was significantly different between both diabetes types ($P_{interaction} = 0.036$). No associations were observed for interleukin (IL)-6, IL-18 and soluble E-selectin. Only the association between HMW/total adiponectin and ADS-L in T2D remained significant after correction for multiple testing.

In conclusion, our study shows that the ratio HMW/total adiponectin is associated with depressive symptoms in individuals with recently diagnosed T2D. It also provides suggestive evidence that further biomarkers of subclinical inflammation and endothelial activation may be associated with depressive symptoms in individuals with recently diagnosed T1D and T2D.

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http://dx.doi.org/10.1016/j.bbi.2016.12.025
0889-1591/

1. Introduction

Depressive disorders represent a frequent comorbidity of both type 1 (T1D) and type 2 diabetes (T2D) (Nouwen et al., 2010; Korczak et al., 2011; Holt et al., 2014). The high prevalence of both depression and diabetes worldwide is characterised by high morbidity and mortality in patients who suffer from both diseases (Korczak et al., 2011; Stuart and Baune, 2012; Holt et al., 2014; Moulton et al., 2015). Different pathophysiological mechanisms have been discussed to link diabetes and depression, such as dysfunction of the hypothalamic-pituitary-adrenal axis, inflammation, neurobiological factors, disturbed circadian rhythm, environmental and behavioural factors (Musselman et al., 2003; Korczak et al., 2011; Stuart and Baune, 2012; Holt et al., 2014; Moulton et al., 2015). The association between depression and diabetes appears complex, because both diseases potentially reinforce one another through a bidirectional temporal and/or causal relationship (Stuart and Baune, 2012). In addition, both diabetes and depression may share common risk factors and pathomechanisms. This could explain some of their comorbid occurrence (Tabak et al., 2014).

Studies in experimental animals and humans identified a close connection between the immune system and neurocircuits in the brain, which may have implications for the role of inflammation in the development of depression (Miller and Raison, 2016). Meta-analyses of cross-sectional studies provided evidence that patients with depression have higher circulating levels of biomarkers of subclinical inflammation, in particular C-reactive protein (CRP), interleukin (IL)-6, IL-1 receptor antagonist (IL-1ra) and tumour necrosis factor (TNF)-α, than non-depressed individuals (Howren et al., 2009; Liu et al., 2012; Hiles et al., 2012a; Haapakoski et al., 2015). This association is supported by prospective studies showing that high levels of CRP and IL-6 are associated with higher risk of developing depressive symptoms and/or clinical depression (Valkanova et al., 2013). A recent meta-analysis of treatment studies also suggested that anti-inflammatory drugs may decrease depressive symptoms, but mean effect estimates were associated with high heterogeneity between the studies and a high risk of bias due to potentially compromised internal validity (Köhler et al., 2014).

There is consistent evidence linking biomarkers of inflammation with depression in community-based and population-based studies. However, there is a limited number of studies that analysed this association specifically in individuals with T2D (Hayashino et al., 2014; Hood et al., 2012; Doyle et al., 2013; Laake et al., 2014) or T1D (Hood et al., 2012). Since the association between inflammation and depression appears to be modulated by the presence of comorbidities such as cardiovascular disease (Howren et al., 2009; Hiles et al., 2012a), findings from the general population cannot be extrapolated to subgroups with specific diseases. This renders further studies in individuals with diabetes as a research priority.

T2D and subclinical inflammation are linked in a bidirectional relationship (Stuart and Baune, 2012). The extent of chronic low-grade immune activation in T2D is exacerbated by the manifestation of macro- and microvascular complications during the progression of the disease (Brownlee, 2001; Kolb and Mandrup-Poulsen, 2005; Donath, 2014). It is currently not clear to what extent inflammatory processes mediate the increased risk of depression in patients with T2D. Furthermore, it remains unclear whether this association is independent of diabetic complications, which are highly prevalent in patients with longer diabetes duration. Additionally, it is not completely clarified whether associations between inflammation and depression are also present in patients with T1D. Both diabetes types share hyperglycaemia as the diagnostic criterion. However, they represent opposite ends of a continuum with different aetiologies, which extends to the contribution of immune activation and inflammation (Leslie et al., 2008).

Therefore, the primary aim of this study was to test the hypothesis that biomarkers of subclinical inflammation were associated with depressive symptoms in patients with recent-onset T2D and T1D after adjustment for multiple confounding factors including diabetes-related comorbidities. The secondary aim of the study was to assess whether these associations differed between both types of diabetes.

2. Study population and methods

2.1. Study population and design

The data are based on the German Diabetes Study (GDS), an ongoing prospective observational study that evaluates the natural history and progression of recent-onset diabetes and its complications (ClinicalTrials.gov identifier NTC01055093) (Szendroedi et al., 2016). The study is being conducted according to the Declaration of Helsinki and was approved by the ethics board of Heinrich Heine University, Düsseldorf, Germany. All participants provided written informed consent.

The study design has been previously published (Szendroedi et al., 2016). Briefly, inclusion criteria for participants were individuals with T1D or T2D, who were diagnosed within less than one year and were between the ages of 18 and 69 years at the time of baseline examination. Diabetes was initially diagnosed by a general practitioner in accordance with the diagnosis guidelines set forth by the American Diabetes Association (2004). The concordance with these criteria was validated before study participation. Exclusion criteria were type 3 diabetes (i.e., diabetes other than T1D or T2D), gestational diabetes, current pregnancy, poor glycaemic control (HbA1c > 9.0%), hyperlipidaemia (triglycerides and low-density lipoproteins ⩾double upper reference limit), evidence of severe congestive heart failure, kidney diseases, liver diseases, symptomatic peripheral arterial disease, venous thromboembolic events, anaemia, blood donation or participation in a clinical study within the past three months, acute infections, leukocytosis, immunosuppressive therapy, autoimmune diseases, infection with human immunodeficiency virus, other severe diseases (e.g. active cancer disease) and psychiatric disorders compromising the ability of the participant to comply with study procedures (Szendroedi et al., 2016).

This cross-sectional analysis was based on all consecutive participants who entered the study between September 2005 and December 2011 (Schamarek et al., 2016; Herder et al., 2017).

2.2. Assessment of depressive symptoms

Depressive symptoms were assessed using the German version of the Center for Epidemiological Studies Depression scale (CES-D), a sensitive instrument to detect depressive symptoms and monitor changes over time (Radloff, 1977; Weissman et al., 1977). The translated German 20-item version is known as Allgemeine Depressionsskala, Langversion (ADS-L) (Hautzinger, 1988). The ADS-L score sums up self-rated responses to 20 questions, which assess symptoms of depression within the previous week on a 4-point scale (from 0 to 3 points). The score ranges between 0 and 60 points, and higher scores indicate a higher number of and/or more frequent depressive symptoms. A cut-off limit score of >22 has been proposed to identify the presence of a depressive disorder (Hautzinger et al., 2012). Psychometric studies demonstrated high internal consistency reliability (Cronbach's alpha 0.85–0.92, Spearman-Brown coefficient 0.86–0.93) Riediger et al., 1998; Hautzinger et al., 2012; Stein and Luppa, 2012). The validity