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Are adverse childhood experiences and depression associated with impaired glucose tolerance in females? An experimental study

Katja Wingenfeld [a, *], Linn K. Kuehl [a], Anita Boeker [b], Katharina Schultebraucks [a], Anne Schulz [a], Julia Stenzel [a], Carsten Spitzer [b, 1], Christian Otte [a, 1]

[a] Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany
[b] Asklepios Fachklinikum Tiefenbrunn, Rosdorf, Germany

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ABSTRACT

Adverse childhood experiences (ACE) enhance the risk for mental disorders, e.g. major depressive disorder (MDD). Increasing evidence suggests an association between ACE and impaired physical health, e.g. metabolic syndrome. The aim of this study was to assess several metabolic risk markers in healthy individuals with and without ACE and depressed patients with and without ACE.

We examined glucose and insulin release in the oGTT in 33 women with MDD and ACE, 47 women with MDD without ACE, 21 women with ACE but no current or lifetime MDD and 36 healthy women without either MDD or ACE. Several metabolic markers such as triglycerides, cholesterol, LDL, HDL, HbA1c, BMI and waist to hip ratio were assessed.

The four groups did neither differ in insulin release and glucose concentrations in the oGTT nor with respect to other metabolic variables. Depressed patients with and without psychotropic medication did not differ in any outcome variable, but there was a trend towards higher glucose concentrations in the oGTT in patients with current psychotropic medication.

In this physically healthy sample neither ACE nor MDD were associated with metabolic risk factors. Thus, metabolic alterations might not directly be linked to ACE and depression.

1. Introduction

Adverse childhood experiences (ACE) have long-term effects on both mental and physical health. Recent research has indicated close associations between ACE and a number of somatic diseases including cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (Afifi et al., 2016; Wegman and Stetler, 2009). Additionally, overweight, high blood pressure, and dyslipidemia, have been linked to early life stress (Tomasdottir et al., 2015). For example, several large cross-sectional studies have reported relations between ACE and diabetes (Goodwin and Stein, 2004; Scott et al., 2011), obesity (Gunstad et al., 2006; Williamson et al., 2002) and hypertension (Afifi et al., 2016; Springer et al., 2007; Stein et al., 2010). Longitudinal studies have confirmed the association between early life stress and obesity (Mamun et al., 2007; Thomas et al., 2008) as well as elevated glycosylated hemoglobin (HbA1c) and T2DM, respectively (Rich-Edwards et al., 2010; Widom et al., 2012). Correspondingly, recent reviews and meta-analyses clearly support an association between ACE, obesity and type 2 diabetes (Danese and Tan, 2014; Huang et al., 2015).

However, beyond this epidemiological evidence there are only few experimental studies that have investigated biological parameters or that have applied challenge tasks to elucidate intermediate processes that occur before disease manifestation. The oral glucose tolerance test (oGTT) allows to determine impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG), both risk factors for developing T2DM, with the highest risk in people with combined IFG and IGT (Unwin et al., 2002). One large cohort study using the oGTT indicated that participants with childhood trauma (war evacuees) had a higher prevalence of T2DM (Alastalo et al., 2009). Interestingly, there were no differences between traumatized and control subjects in body mass index (BMI), triglycerides and high-density lipoprotein (HDL). However, to the best of our knowledge there is no study investigating insulin and glucose

* Corresponding author. Department of Psychiatry and Psychotherapy, Charité University Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, 12203 Berlin, Germany.
E-mail address: katja.wingenfeld@charite.de (K. Wingenfeld).
[1] Equal contribution.

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concentrations in the oGTT in physically healthy adults with a history of childhood abuse.

There is also a close link between ACE and major depressive disorders (MDD) (Mandelli et al., 2015), which in turn is associated with metabolic alterations, diabetes and CVD (Mezuk et al., 2008; Muhtz et al., 2009; Otte et al., 2016; Penninx et al., 2013; Seppala et al., 2012; van Reedt Dortland et al., 2010). Although individuals with MDD seem to be more prone to develop diabetes (Fiore et al., 2015), there are only few studies relating the oGTT to depression (Golden et al., 2008). Compared to non-depressed controls, patients with MDD were reported to have significantly reduced insulin sensitivity (Hung et al., 2007). However, in this study the area under the curve for insulin and glucose in the oGTT did not differ between patients and controls. In contrast, Li and colleagues found that fasting and 2-h glucose concentrations remained within the normal range through compensatory insulin secretion in MDD patients (Li et al., 2016). Another study found increased insulin and glucose concentrations in the oGTT in MDD patients (Hennings et al., 2010), while others reported only higher glucose levels (Garcia-Rizo et al., 2013). Notably, these studies only investigated relatively small samples including 10–21 patients, which may limit conclusions. A large study investigating more than 400 patients with a depressive episode indicated that depressed patients with suicidal behavior had higher baseline glucose as well as higher glucose levels in the oGTT than non-suicidal depressed participants (Koponen et al., 2015). Unfortunately, no healthy control group was assessed. Interestingly, in a large population based sample (N = 1.047) without diabetes, depressive symptoms were not found to be associated with impaired glucose tolerance (Rhee et al., 2008).

In sum, several lines of evidence suggest that both childhood adversities and MDD may lead to in an increased risk for T2DM and other features of metabolic syndrome. Particularly, their complex interplay might amplify the risk for alterations subsequently leading to obesity, diabetes and metabolic syndrome (Danese and Tan, 2014; Scott et al., 2011; Stein et al., 2010). However, no study so far has systematically tried to disentangle the influence of ACE and MDD on metabolic risk factors. Thus, the current study focused on insulin and glucose concentrations in the oGTT in healthy individuals with and without ACE and depressed patients with and without ACE. Of note, we only included physically healthy individuals without obesity, because it is closely related to prediabetes and T2DM (Jaacks et al., 2016). This is important as we aimed to study whether ACE and depression are risk factors for the development of metabolic symptoms. Moreover, we restricted our sample to women because of sex differences in response to the oGTT and the metabolic syndrome (Regitz-Zagrosek et al., 2006; Sicree et al., 2008). In line with the above mentioned findings, we hypothesized patients with MDD and ACE to have the highest glucose and insulin concentrations after glucose intake. Patients with MDD without ACE as well as healthy individual reporting ACE will show moderate changes compared to healthy individuals without ACE and without depression. Furthermore, we hypothesized that changes in metabolic risk factors, as triglycerides, cholesterol and HbA1c will be most pronounced in the group of depressed patients with ACE.

2. Methods and material

2.1. Participants

We recruited 33 women with MDD and ACE (MDD+/ACE+), 47 women with MDD without ACE (MDD+/ACE−), 21 women with ACE but no current or lifetime MDD (MDD−/ACE+) and 36 healthy women who had never had any mental disorder and did not report sexual or physical abuse (MDD−/ACE−). ACE was defined as repeated sexual or physical abuse at least once a month over one year or more before age of 18. We decided only to recruit women, as the prevalence of childhood sexual trauma is higher in women compared to men.

Before testing all participants underwent a comprehensive clinical assessment, including the Structured Clinical Interview for DSM-IV axis I and II to validate psychiatric diagnoses. Furthermore, we used a semi-structured interview, the Early Trauma Inventory (Bremner et al., 2000; Wingenfeld et al., 2011) and the Childhood Trauma Questionnaire (CTQ) (Bernstein et al., 2003; Wingenfeld et al., 2010) to assess childhood trauma.

Healthy participants with and without ACE were free of any current mental disorder. All MDD patients met DSM-IV diagnosis of current major depressive disorder. In the MDD groups schizophrenia, schizoaffective disorder, bipolar disorder, depressive disorder with psychotic features, anorexia, alcohol or drug dependence led to exclusion. In addition to the SCID-I interview, current depressive symptoms were captured by clinical interview and questionnaire, the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979; Williams and Kobak, 2008) and the Beck Depression Inventory (BDI) (Beck et al., 1996).

Further exclusion criteria for all participants were CNS diseases or severe somatic diseases, diabetes type 1 and 2, or endocrine and autoimmune diseases, current infections, or pregnancy and a body mass index (BMI) higher than 30.

The study took place at the Department of Psychiatry, Charité - Universitätsmedizin Berlin, Campus Benjamin Franklin, Berlin, Germany and the Asklepios Fachklinikum Tiefenbrunn. Participants were recruited by public posting and from our specialized affective disorder clinics at Charité and Tiefenbrunn. Fourty-two patients with MDD (12 MDD+/ACE+, 30 MDD+/ACE−) were inpatients, while the remaining 38 MDD patients were outpatients recruited by public posting, e.g. internet and notices at sexual assault service providers. In addition, healthy individuals were recruited via student email lists, internet advertisements and via our Charité research website.

All participants provided written informed consent. Healthy control participants and outpatients received monetary remuneration (€200) for their participation. The study was approved by the local ethical committee.

2.2. Procedures and measures

Participants arrived at the laboratory at 8 a.m. after an overnight fast. Height, weight as well as waist and hip circumference were assessed and blood pressure was measured. Afterwards an intravenous catheter was inserted and blood was collected for measurement of triglycerides, cholesterol, LDL (low density lipoprotein), HDL (high density lipoprotein) (plasma) as well as HbA1c (EDTA blood).

All participants underwent a standardized oral glucose tolerance test (oGTT) beginning at 9:00 a.m. Immediately after the first blood sample (baseline, 0 min) 75 g (300 ml “ACCU-CHEK Dextrose O.G.-T. Saft”, Roche) was given orally. Further blood samples for measurement of glucose (plasma) and insulin (serum) were drawn after 30, 60, 90 and 120 min. According to the WHO definition glucose concentrations ≥140 mg/dl after 2 h are interpreted as disturbed glucose tolerance (www.who.int). Blood samples were analyzed at the “Labor Berlin - Charité Vivantes GmbH”.

Following the International Diabetes Federation (IDF, http://www.idf.org/metabolic-syndrome) metabolic syndrome was defined as meeting at least three of the following criteria including central obesity: waist circumference ≥ 80 cm, triglycerides ≥ 150 mg/dl, HDL < 50 mg/dl, systolic blood