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Suboptimal glycemic control in type 2 diabetes: A key role for anhedonia?

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ABSTRACT

Recent studies examining the relationship between depression and glycosylated hemoglobin (HbA_{1c}) concentrations in patients with type 2 diabetes have yielded mixed findings. One explanation may lie in the heterogeneity of depression. Therefore, we examined whether distinct features of depression were differentially associated with suboptimal glycemic control.

Cross-sectional baseline data from a dynamic cohort study of primary care patients with type 2 diabetes from the Eindhoven region, The Netherlands, were analyzed. A total of 5772 individuals completed baseline measurements of demographic, clinical, lifestyle and psychological factors between 2005 and 2009. The Edinburgh Depression Scale was used to assess symptoms of depressed mood, anhedonia and anxiety. Suboptimal glycemic control was defined as HbA_{1c} values $\geq$7%, with 29.8% of the sample ($n = 1718$) scoring above this cut-off. In univariate logistic regression analyses, anhedonia was significantly associated with suboptimal glycemic control (OR 1.29, 95% CI 1.09–1.52), while both depressed mood (OR 1.04, 0.88–1.22) and anxiety (OR 0.99, 0.83–1.19) were not. The association between anhedonia and glycemic control remained after adjustment for the other depression measures (OR 1.33, 1.11–1.59). Alcohol consumption and physical activity met criteria for mediation, but did not attenuate the association between anhedonia and glycemic control by more than 5%. Although diabetes duration was identified as a confounder and controlled for, the association was still significant (OR 1.20, 1.01–1.43). Studying different symptoms of depression, in particular anhedonia, may add to a better understanding of the relationship between depression and glycemic control.

1. Introduction

Depressive symptoms are common among individuals with type 2 diabetes, affecting up to 30% of patients (Ali et al., 2006). A growing number of studies indicate that depressed diabetes patients are at increased risk for various adverse health outcomes, including the development of macro- and microvascular complications and higher mortality rates (Black et al., 2003; Lin et al., 2010). Findings regarding the association between depression and glycemic control are less consistent. Although a meta-analysis based on 24 cross-sectional studies published up until 1999 concluded that depression was significantly associated with higher glycosylated hemoglobin (HbA_{1c}) concentrations (effect size 0.17, 95% CI 0.13–0.21) (Lustman et al., 2000), subsequent studies in patients with type 2 diabetes have yielded mixed results (Fisher et al., 2010).

One explanation may lie in the heterogeneity of depression. Rather than encompassing a homogeneous condition, depression is characterized by a variety of symptoms and subtypes, which do not all have to be present in individual patients (Stein, 2008). Core characteristics range from depressed mood (dysphoria) to a loss of interest or pleasure (anhedonia), and additional symptoms may even include anxiety (DSM-IV-TR, 2000). While dysphoria comprises negative emotions such as feelings of sadness and emptiness, anhedonia is often conceptualized as a condition in which positive affect is reduced (Nutt et al., 2007). Low positive affect has been associated with a higher risk of cardiovascular conditions and mortality in community-dwelling elderly and patients with established coronary artery disease (Blazer & Hybels, 2004; Davidson et al., 2010; Denollet et al., 2008; Leroy et al., 2010; Ostir et al., 2001) and was found to predict all-cause mortality in people with diabetes (Moskowitz et al., 2008). A small study in

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older women without diabetes showed an adverse effect of low positive affect on HbA_{1c} levels (Tsenkova et al., 2008), but this association has not been examined in patients who already have diabetes.

Therefore, the primary aim of this study was to explore whether the two core features of depression – dysphoria and anhedonia – are differentially associated with suboptimal glycemic control. Knowing that anxiety symptoms may figure prominently in depression and appear to adversely affect patient outcomes (Barbee, 1998), anxiety was included in the analyses as a second measure of negative affect. As the mechanisms behind the association between emotional distress and glycemic control are still unclear but likely include less adequate self-care behaviors (Gonzalez et al., 2008), we also examined the role of body mass index and several health behaviors as potential mediators of these associations.

2. Materials and methods

2.1. Study sample

The DIAZOB Primary Care Diabetes study is an ongoing dynamic cohort study in primary care patients with type 2 diabetes and is conducted in collaboration with over 200 general practitioners from the Eindhoven region (The Netherlands). Measurements include the annual assessment of a broad range of demographic, medical, lifestyle and psychosocial factors and are performed within the framework of the DIAZOB (Diabetes care Zuidoost-Brabant) standard care project, a diabetes management programme for patients with type 2 diabetes in which a primary care practice nurse provides regular diabetes care. Within DIAZOB, diabetes is diagnosed according to the guidelines of the Dutch College of General Practitioners. These criteria are comparable to the current recommendations of the American Diabetes Association. A more detailed description of the DIAZOB Primary Care Diabetes study and related projects can be found elsewhere (Nefs et al., 2010). The present study includes cross-sectional baseline data from 5772 patients with type 2 diabetes who joined DIAZOB between April 2005 and January 2009 and had complete data regarding gender, age, HbA_{1c} and depressive symptoms. These patients did not differ significantly from those with missing depression data ($n = 6405$) with respect to gender (48.6% versus 50.3% women, $p = 0.060$), but were somewhat older (mean age 66.8 versus 66.4 years, $p = 0.045$) and had a clinically irrelevant, slightly lower mean HbA_{1c} (6.72 versus 6.75, $p = 0.044$). The study was approved by the medical research ethics committee of a local hospital, the Máxima Medical Center Veldhoven. Written informed consent was obtained from all participants.

2.2. Suboptimal glycemic control

Suboptimal glycemic control was defined as HbA_{1c} values $\geq$7%, in line with the Dutch Primary Care Guidelines for type 2 diabetes. HbA_{1c} was assessed at the Diagnostic Center Eindhoven (a primary care diagnostic laboratory), the Elkerliek Hospital Deurne/Helmond and the St. Anna Hospital Geldrop, using ion-exchange high performance liquid chromatography.

2.3. Depressive symptoms

Presence of the two key elements of depression (dysphoria, anhedonia) and additional symptoms of anxiety during the last seven days was assessed using a validated Dutch version of the Edinburgh Depression Scale (EDS) (Pop et al., 1992). The EDS is a 10-item self-rating scale in which each item is scored on a four-point scale, with total scores ranging from 0 to 30 points. Even though the EDS was originally designed to assess postpartum depression, later evidence showed that it is also valid for use in other (male and female) strata (Becht et al., 2001; Cox et al., 1996; Matthey et al., 2001; Nyklicek et al., 2004). It has become clear that the EDS actually measures three different symptom dimensions: depressed mood (4 items: e.g. "I have felt sad or miserable", "I have been so unhappy that I have been crying"), anhedonia (2 items: "I have been able to laugh and see the funny side of things", "I have looked forward with enjoyment to things"), and anxiety (3 items: e.g. "I have been anxious or worried for no good reason", "I have felt scared or panicky for no very good reason") (Tuohy & McVey, 2008). In the present study, the Cronbach's alpha of the different subscales was 0.76, 0.78 and 0.70, respectively. As the previously published cut-off values of the ten-item EDS (usually $\geq$12) (Becht et al., 2001; Cox et al., 1996; Nyklicek et al., 2004) generally correspond to the upper 90th percentile score, high scores on its subscales were also defined using the 90th percentile cut-off (depressed mood $\geq$4, anhedonia $\geq$3; anxiety $\geq$6) in this study.

2.4. Potential demographic, clinical and lifestyle-related confounding or mediating factors

Information regarding age, sex, ethnicity (Caucasian versus non-Caucasian), educational level (middle/high versus low education), diabetes duration (less than three years versus three years or more) and health behaviors was obtained by a nurse-led interview and a self-report questionnaire. Lifestyle factors included smoking status (no versus one or more cigarettes/day), alcohol intake (14 or less versus more than 14 drinks/week) and physical activity as defined by hours of "active" (daily activities including gardening, walking, climbing stairs) and "sportive" activities (e.g., sports, fitness) per week. Patients' body mass index (BMI; weight in kilograms/length in meters^2) was derived from standard care physical examinations. BMI was dichotomized into BMI $<$ 30 versus $\geq$30 kg/m^2. Dichotomization of variables was employed to improve clinical interpretability by allowing a comparison of low-medium versus high risk groups based on several Dutch and international health care guidelines (International Center for Alcohol Policies, 2003; Wendel-Vos & van Gool, 2008; World Health Organization, 2000).

2.5. Statistical analyses

A confirmatory factor analysis was used to examine the fit of the three factor EDS structure (depressed mood, anhedonia, anxiety) to our data. Demographic, clinical and lifestyle characteristics of patients with and without high levels of symptoms on the three subscales of the EDS were compared using X^2 tests (dichotomous variables) and independent samples t-tests (continuous variables). To test whether the EDS subscales were associated with suboptimal HbA_{1c}, univariate logistic regression analyses were performed, followed by a multivariate model in which all measures of emotional distress were entered simultaneously. In case we found a significant association between an EDS subscale and HbA_{1c}, several candidate confounders or mediators were examined.

To establish mediation, selected variables (BMI, smoking, alcohol consumption and the two measures of physical activity) had to meet the four mediation criteria formulated by Baron and Kenny (Baron & Kenny, 1986). To this end, a series of logistic regression analyses was conducted. In a first step, the independent variable had to be associated with the mediator (regressing the candidate mediator on the EDS subscale). Second, the independent variable had to be associated with the dependent variable (as was done in the previously mentioned univariate analyses, by