



Depressive Symptoms Associated With Mortality in Patients With Type 1 Diabetes

Written by Kate Mann

The presence of depressive symptoms at baseline and over time was associated with an increased risk of mortality in men and women with type 1 diabetes mellitus (T1DM) in an analysis of data from the Epidemiology of Diabetes Complications study [EDC; Pambianco G et al. *Diabetes* 2006], presented by Catherine E. Fickley, MPH, University of Pittsburgh, Pittsburgh, Pennsylvania, USA.

The prevalence of clinical depression in patients with T1DM was 12% compared with 3% in healthy controls in a meta-analysis [Barnard KD et al. *Diabet Med* 2006]. The existing literature on the relation between depression and depressive symptoms and diabetes outcomes in patients with T1DM appears to be limited to one study that showed a relation between depression, as measured by antidepressant use, and an increased risk of mortality in women but not in men [Ahola AJ et al. *Diabetologia* 2012]. A relationship between depression and increased mortality in the general population and in patients with type 2 diabetes mellitus (T2DM) has been reported.

The EDC is a prospective cohort study of 658 participants with childhood-onset T1DM who have been followed since 1986. At baseline, their mean age was 28 years (range, 8 to 48 years) and diabetes duration was 19 years (range, 7 to 37 years). At baseline, the Beck Depression Inventory (BDI) questionnaire was completed by participants. The BDI includes items related to symptoms of depression, cognition, and physical symptoms.

In total, 458 (235 women, 223 men) participants who completed the BDI at baseline were eligible for this analysis, in which investigators examined whether the incidence of all-cause mortality varied according to reported depressive symptoms over time while controlling for relevant covariates.

During the 20-year follow-up, 94 deaths (43 women, 51 men) occurred. The BDI score was associated with mortality on univariate analysis (HR, 1.39; 95% CI, 1.23 to 1.58; $p < .001$).

The association between depressive symptoms and mortality persisted (HR, 1.35; 95% CI, 1.17 to 1.56; $p < .001$) on multivariable analysis, adjusted for T1DM duration, calories consumed, total cholesterol, waist-to-hip ratio, HbA1C, education, hypertension, blood pressure medication, type A behavior, coronary artery disease, white blood cell count, and calories consumed, among others.

The use of antidepressants was not a confounding variable and only slightly diminished the association

between depressive symptoms and mortality risk (HR, 1.32; 95% CI, 1.14 to 1.54; $p < .001$). No association was found between depressive symptoms and mortality risk between women and men ($p = .02$) or between sex and antidepressant use ($p = .81$).

When a cut point of 16 for clinically important depression was used, a significant relation between mortality and a BDI 16 or higher was found compared with a BDI less than 16 (HR, 2.87; 95% CI, 1.83 to 4.50; $p < .001$).

A strength of this analysis was that the self-reported BDI captured depressive symptoms in patients who were and were not taking antidepressants, stated Fickley. Depressive symptoms over time predicted mortality in both women and men in this analysis, regardless of antidepressant use. These data support the need to evaluate efforts to improve screening and treatment of depression in T1DM.

PTA Is Effective and Safe for Patients With Type 1 Diabetes

Written by Brian Hoyle

Researchers have demonstrated in a decadelong study that pancreas transplantation alone (PTA) can be effective and safe for patients with type 1 diabetes mellitus (T1DM), with the caveat that this advance benefits select, not all, patients with T1DM. The findings were reported by Margherita Occhipinti, MD, University of Pisa, Pisa, Italy.

PTA was first reported in the late 1960s. Advances in areas including immunosuppressive therapy have considerably improved patient outcomes [Gruessner RWG, Gruessner AC. *Diabetes Care* 2013]. Still, the long-term outlook is unclear. In the Pisa group, experience with pancreas and kidney transplantation dates back to the development of PTA, with 355 PTA procedures having been performed in 337 patients. This study sought to determine the actual 10-year PTA results in this single center.

The study involved 34 patients (17 men, 17 women) who underwent PTA from December 2000 to December 2003. The patients were aged 37 ± 9 years, had a body mass index of 23.5 ± 3.3 kg/m² and a duration of diabetes of 23 ± 10 years, and received 47 ± 10 U of insulin daily. All patients were transplanted by use of the portal-enteric drainage approach. Immunosuppressive therapy consisted of basiliximab (20 mg on Days 0 and 4) and high-dose steroids. Maintenance therapy consisted of tacrolimus, mycophenolate, and low-dose steroids.

The 10-year data revealed patient and pancreas survival rates of 97.0% and 63.6%, respectively, representing 1 death due to stroke (graft functional at time of death)

and 12 cases of graft failure due to acute rejection in 2 patients and chronic rejection in 10 patients.

Blood levels of tacrolimus at 6 months and 10 years were 11.53 ng/mL and 8.72 ng/mL, respectively. Mycophenolate mofetil was used exclusively through 6 months (2000 mg/day), but by 10 years sodium mycophenolate 750 mg/day was used in 60% and mycophenolate mofetil 1250 mg/day in 40% of patients. Steroid use declined from 97% of patients at 6 months to 88% of patients at 5 years to 42% of patients at 10 years. C-peptide increased markedly from commencement of treatment in the first year and remained the same thereafter. Fasting plasma glucose and HbA1C declined at about 1 year and then remained constant. Comparisons of patients prior to surgery and at 10 years revealed significant decreases in total cholesterol and low-density lipoprotein cholesterol (LDL-C; $p < .001$ for both), with insignificant declines in high-density lipoprotein cholesterol and triglyceride.

Blood pressure (BP) measurements demonstrated significant declines from baseline in systolic BP at 1 and 5 years, and in diastolic BP only at 1 year. The left ventricular ejection fraction (LVEF) significantly increased from 54% at baseline to 59% at 10 years ($p < .001$). Kidney function declined by a mean 1.8 ± 2 mL/min annually; the overall decrease was not significant.

In this 10-year study, pancreas transplant alone was associated with satisfactory long-term patient and graft control, long-term restoration of endogenous insulin secretion and normalization of glycemic control, significant improvement in levels of total cholesterol and low-density lipoprotein, improved left ventricular ejection fraction, and a level of kidney function judged to be reasonable. Thus, the approach was concluded to be safe and effective for selected patients with T1DM.

Impaired Awareness of Hypoglycemia Mapped to Less Activation of Brain Regions Involved in Stress Response

Written by Kate Mann

Pratik Choudhary, MD, King's College London, London, United Kingdom, presented data showing that men with type 1 diabetes mellitus (T1DM) with impaired hypoglycemia awareness (HA) have different brain activation patterns than do patients with intact HA. Patients with T1DM who are unable to sense that they are hypoglycemic have less activation of brain regions involved in the stress response, autonomic activation, and emotional salience.

Hypoglycemia is a huge burden for patients with T1DM. Epidemiologic and cross-sectional studies suggest that 25% to 40% of patients with T1DM have impaired HA, and the incidence increases as the disease duration increases [Choudhary P et al. *Diabet Med* 2010]. Impaired HA increases the risk of severe hypoglycemia by 3 to 6 times [Choudhary P et al. *Diabet Med* 2010] and is associated with counterregulatory hormonal and symptomatic responses to subsequent hypoglycemia.

Dr. Choudhary and his colleagues previously published findings on the evolution of brain responses to acute hypoglycemia in nondiabetic healthy volunteers using water positron-emission tomography (PET) imaging, showing that different regions of the brain were engaged in response to different stressors [Teh MM et al. *Neuroimage* 2010]. The objective of the current study was to compare regional brain activation during experimental hypoglycemia in people with T1DM and intact or impaired HA, using radiolabeled water PET scanning. The researchers used hyperinsulinemic clamping to achieve a succession of glycemic states: euglycemia (90 mg/dL), hypoglycemia (46.8 mg/dL for 50 minutes), and recovery (90 mg/dL). Scans were performed at 10-minute intervals before, during, and up to 40 minutes after hypoglycemia.

In total, 27 right-handed men were studied (17 men with T1DM with >5 years' duration of diabetes, of whom 8 had impaired HA, and 10 healthy controls). The patients with T1DM were older and heavier than were the healthy volunteers, although those with intact and impaired HA were well matched (Table 1). A Clarke score ≥ 4 indicates impaired HA.

Table 1. Baseline Characteristics in Study Subjects

	Healthy Controls	Hypoglycemia Awareness	
		Intact	Impaired
Number	10	9	8
Mean age, years	27.7	37.1	35.3
Body mass index, kg/m ²	22.3	23.6	26.5
A1C, %	N/A	7.8	7.4
Diabetes duration, years	N/A	13.8	23.2
Clarke score	N/A	1.4	5.3

N/A=not applicable.

Among T1DM subjects with impaired HA compared with subjects with intact HA or healthy volunteers, acute hypoglycemia resulted in deactivation or lack of activation in brain regions involved in stress responses,