Why Are Diabetes and Depression Associated?

Connecting the Brain to the Pancreas

Sherita Hill Golden, MD, MHS
Hugh P. McCormick Family Professor of Endocrinology and Metabolism
Executive Vice-Chair, Department of Medicine

Division of Endocrinology, Diabetes, and Metabolism
Welch Center for Prevention, Epidemiology, and Clinical Research
Birth of a Research Career

San Antonio, TX
American Diabetes Association Meeting 2000

Dr. Fred Brancati
Edvard Munch, 1893
• You added bleach to the color load by accident!

• You woke up at the time you were supposed to be leaving for work!

• Most of your writers have not submitted their articles for a pending deadline!
William Osler, MD
First Chairman of Medicine
Johns Hopkins University
Risk Factors for Type 2 Diabetes

Osler’s Principles & Practice of Medicine, 1892

- Heredity
- Ethnicity
- Social Class
- Adiposity
- Sedentary life
- Overindulgence

- Nervous strain
- Worry

STRESS

STRESS
Diabetes and Depression: A Common Association In Adults

- Aggregate odds ratio of depression in adults with diabetes compared to those without diabetes: 2.0 (95% CI: 1.8, 2.2)

- Lifetime prevalence of major depression higher in individuals with diabetes (17.5%) compared to those without diabetes (6.8%)

Anderson et al. Diabetes Care, 2001
Diabetes and Depression: A Common Association in Adolescents

- 15-20% of adolescents with type 1 diabetes have elevated depressive symptoms
- 23% have subclinical depressive symptoms
- SEARCH Study: rates similar for type 1 and type 2 diabetes, but slightly higher in type 2

Kovacs et al., 1997; Grey et al, 2002; Hood et al., 2006; McGrady et al., 2009; Lawrence et al., 2006
Average Ages of Onset for Diabetes and Depression

Type 1 DM
5-14

Depression
18 - 39

Type 2 DM
40-60

Depression
45 - 64

From Dr. Mercedes Carnethon
Diabetes mellitus → DEPRESSION
Psychological demands imposed by diabetes

DIABETES

New complications

Multiple complications
Visual impairment
Impotence
Impaired physical/cognitive functioning

Lack of social support

Passive coping skills

DEPRESSION
Hyperglycemia associated with diabetes

HYPERGLYCEMIA

• Adverse effects on hippocampus
  – Atrophy
  – Neuronal apoptosis

• Brain region that controls mood and cognition
Description of the Multi-Ethnic Study of Atherosclerosis (MESA)

• Multi-center, longitudinal cohort study of occurrence and correlates of subclinical CVD and factors influencing its progression

• Six centers: Northwestern University, Wake Forest University, University of Minnesota, Columbia University, Johns Hopkins University, University of California-Los

• 6,000 men and women aged 45-85 years
  – 40% non-Hispanic White
  – 10% Chinese American
  – 30% African American
  – 20% Hispanic American
  – No history of clinical CVD
MESA: Diabetes ➔ Depression

Visit 1 (00-02)
Visit 2 (02-04)
Visit 3 (04-05)

4,847 adults aged 45 to 84 w/o prevalent depression or CHD

Glucose Status
- Normal fasting glucose (NGT)
- Impaired fasting glucose (IFG)
- Untreated DM
- Treated DM

Depression
- CES-D ≥ 16 and/or anti-depressant use
Diabetes Predict Development of Depression

- Individuals with diabetes at baseline had a 50% higher risk of developing depression during follow-up compared to those without diabetes.

- Independent of differences in diabetes complications, socioeconomic status, and obesity.

Golden et al, *JAMA*, 2008
**Depression**

- **Psychosocial**
  - burden of illness, social support

- **Behavioral**
  - smoking, diet, physical activity, treatment adherence

- **Treatment**
  - Serotonin reuptake inhibitors
  - Tricyclics

- **Neurohormonal**
  - ↑cortisol, ↑catecholamines, ↑inflammatory markers

**Obesity**

**Insulin Resistance**

**Type 2 Diabetes**
MESA: Depression  Diabetes

Visit 1
00-02

Visit 2
02-04

Visit 3
04-05

5,201 adults ages 45 to 84 w/o prevalent diabetes or CHD

Depression
CES-D \geq 16 and/or anti-depressant use

TYPE 2 DM
Depression Predicts Development of Diabetes

Depression was associated with type 2 diabetes risk factors:

- Less physical activity
- Greater calorie intake
- Higher likelihood of current smoking
- Higher body mass index
- High levels of inflammatory markers

After controlling for these factors, depression was associated with a 21% higher risk of developing type 2 diabetes

Golden et al, *JAMA*, 2008
Linking the Brain and Pituitary to the Pancreas?
Stress affects hormonal factors that increase diabetes risk

Depression/Stress

HPA axis hyperactivity

SNS activation

↑ catecholamines

↑ interleukin-6

↑ cortisol

CENTRAL OBESITY

INSULIN RESISTANCE

TYPE 2 DM

Harrison’s Textbook of Internal Medicine
Metabolic Perils of Central Obesity

- ↑ glucose and insulin resistance
- ↑ blood pressure
- ↑ dyslipidemia (high triglycerides, low HDL)
- Risk for developing type 2 diabetes
Insulin Regulates Glucose Metabolism

Normal insulin action

Glucose, other food molecules

Energy

Abnormal insulin action

Glucose, other food molecules

No energy!
Cortisol Hypothesis: Animal Data

11 \( \beta \)-HSD 1 inactive active cortisol

Transgenic mouse model of 11\( \beta \)-HSD1 overexpression
- Insulin resistance
- Obesity
- High cortisol in liver circulation

Cortisol Hypothesis: Clinical and Human Research Data

- **Overt hypercortisolism**
  - Cushings’ Syndrome
  - Steroid-induced diabetes

- **Cortisol axis dysfunction independent of depression**
  - Type 2 diabetes
  - Obesity

Champaneri et al, Metabolism, 2012
Champaneri et al, Obesity, 2013;
Joseph et al, Psychoneuroendocrinology, 2015
So What? Significance and Future Directions

- Modification of the neurohormonal response: a novel approach to primary prevention of Type 2 diabetes (complementary to established measures)

- Collaborative care models that simultaneously treat depression and diabetes will likely improve outcomes for both conditions
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