THE MENTAL HEALTH COMORBIDITIES OF DIABETES
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DISCLOSURES
1. I do not have any conflicts of interest or financial disclosures
2. To receive contact hours for this continuing education activity, the participant must:
   1. Attend the entire session
   2. Complete the program evaluation at the completion of the event

OBJECTIVES
1. Diabetes and mental health
2. The comorbidity between diabetes and psychiatric conditions
3. Potential mechanisms linking mental illness and diabetes
4. Clinical implications for patient’s care
COMORBIDITY BETWEEN MEDICAL AND MENTAL CONDITIONS

2001-2003 National Comorbidity Survey Replication

- more than 68% of adults with a diagnosed mental disorder have at least one general medical disorder
- 29% of adults with a medical disorder have a comorbid mental health condition

Alegria M et al. Ann Arbor Inter-university Consortium for Political and Social Research, 2003

- 25% of American adult population (one in four) meet criteria for at least one diagnosable mental disorder in any given year
- more than half report one or more chronic general medical conditions

Alegria M et al. Ann Arbor Inter-university Consortium for Political and Social Research, 2003

COMORBIDITY BETWEEN MEDICAL AND MENTAL CONDITIONS

Mental health and medical conditions are risk factors for each other and the presence of one can complicate the treatment of the other (each type of disorder is a risk factor for developing the other).

When mental and medical conditions co-occur, the combination is associated with elevated symptoms burden, functional impairment, decreased length and quality of life, and increased costs.

Carney CP et al. Journal of General Internal Medicine, 21(11), 2006
Carney CP et al. Psychosomatic Medicine, 68(5), 2006
Egede LE. General Hospital Psychiatry, Vol 29, No. 5, 2007
Stein MB et al. Psychological Medicine, Vol 36, No. 5, 2006
DIABETES AND MENTAL HEALTH

Diabetes mellitus (DM) and mental illnesses are prevalent, disabling, and highly co-occurring diseases.

DM is considered to be one of the most psychologically demanding of the chronic medical illnesses and is often associated with psychiatric disorders.

Thomas Willis - diabetes was caused by “long sorrow and other depressions”.

Sir Henry Maudsley - “Diabetes is a disease which often shows itself in families in which insanity prevails.”

The rate of DM, an important cardiovascular risk factor and cause of mortality itself, is increased by twofold to threefold in patients with mental illnesses.

The age of onset of DM in individuals with mental illnesses is 10-20 years lower than that in general population.

In people with mental illnesses, the consequences of DM are more severe than in those without a mental illness, with higher rates of vascular complications, acute metabolic dysregulation and deaths related to DM.
DIABETES AND MENTAL HEALTH

Obtaining the precise prevalence rates of DM in people with mental illness is challenging because of the high level of undiagnosed diabetes in this population.

Exactly when the increased risk of DM begins to manifest in patients with mental illness is controversial, with some studies showing subtle metabolic abnormalities before patients begin pharmacological treatment.

The majority of studies suggest that metabolic abnormalities accumulate rapidly after the initiation of treatment.


DIABETES AND MENTAL HEALTH

The patients with DM and mental health comorbidities have:

- poorer clinical outcomes and prognosis
- adverse health-behaviors and poor self-care
- impaired quality of life
- increased in health services costs


DIABETES AND MENTAL HEALTH

Psychological factors in DM

1. acceptance of diagnosis, denial and uncertainty
2. fear of hypoglycemia
3. fear of complications
4. adherence
DIABETES AND MENTAL HEALTH

DM is a demanding health-related condition and up to almost 50% of diabetic patients suffer from emotional distress caused by different stressors:
- burden of caring for DM - managing complications, adhering to dietary restrictions, monitoring glucose levels
- life stressors - family, work, financial
- other causes - personal characteristics, life history


DIABETES AND MENTAL HEALTH

Distinguishing between diabetes distress and major depressive disorder (MDD) is important because the psychological experiences in people with DM are different and may be most strongly related to adverse diabetes outcomes.

Diabetes distress occurs more frequent than MDD and is associated with poor adherence to treatment, glycemic control, higher rates of DM complications and impaired quality of life.


DIABETES AND PSYCHIATRIC CONDITIONS

DM was reported to be comorbid with the following mental illnesses:
- depression
- psychotic disorder
- bipolar disorder
- anxiety disorder
- eating disorder
DIABETES AND DEPRESSION

Centers of Disease Control and Prevention (CDC)
- more than 10% of US adults have DM
- MDD affects approximately 6.7% of the US population

The odds of having depression is twice as great in patients with DM comparing with those without it.

http://www.cdc.gov/diabetes/pubs/factsheet07.htm
Wayne JK. The American Journal of Medicine. 121 (S8-S15), 2008

DIABETES AND DEPRESSION

The prevalence rate of depression is more than three-times higher in people with type 1 diabetes and nearly twice as high in people with type 2 diabetes compared to those without this medical condition.

2002 World Health Survey - prevalence of 8% of depression in patients with no DM comparing with 20% prevalence in patients who have this medical condition.

Roy T et al. Journal of Affective Disorders. 142, 30-52, 2013
McCarty M et al. Diabetes Medicine. 30(6), e208-e214, 2013

DIABETES AND DEPRESSION

Depression has the greatest disability in health when compared with other chronic conditions.

The combination of DM and depression is the most disabling of the comorbidities.

Patients with major depression and DM are 1.5 - 2 fold more likely to have 3 or more cardiovascular risk factors than patients with diabetes without depression.

Holt RI et al. J Affect Disord. 142 (S1-S3), 2012
Moussavi S et al. Lancet. 370 (8518), 2007
DIABETES AND DEPRESSION

Comorbid depression in patients with DM is associated with:

- increased numbers and severity of diabetic symptoms and complications (retinopathy, nephropathy, neuropathy, sexual dysfunction and vascular complications)
- higher rates of functional disability and premature mortality
- worse adherence to multiple components of diabetes treatment recommendations including missed medical appointments, medication use, glucose monitoring, and foot care

Egede LE et al. Diabetes Care, 26 (108-114), 2005

The course of depression in patients with DM is chronic and severe.
- Episodes of MDD in individuals with DM are likely to last longer and have a higher chance of recurrence compared to those without DM.
- 80% of patients with diabetes will experience depression relapse.


Bidirectional association:
- people with DM are more likely to develop depression than those without this medical condition
- up to 60% increased risk for developing type 2 diabetes in people with depression at baseline
- depression is an independent risk factor for the onset of DM and a predictive factor for the number and severity of diabetic complications

Eaton WW et al. Diabetes Care, 19, 1097-1102, 1996
**DIABETES AND DEPRESSION**

Risk factors for depression specific to DM include:

- presence of diabetic complications
- presence of comorbidities
- knowledge of having DM
- smoking
- perceived burden of DM
- duration of DM
- use of insulin
- persistent poor glycemic control
- treatment intensity

Mantyselka et al. Diabetes Care, 34:71-6, 2011

**DIABETES AND SUICIDE**

Suicidal ideations and attempts are more frequent in patients with DM than healthy or medically ill control.

The rates of suicidal ideations and suicidal attempts has been reported to be as high as 26.4% and 13.3%, respectively.

Depression has been reported to be the most common psychiatric disorder in persons with DM who attempted suicide.

Roy A et al. Psychiatry Res, 179:53-6, 2010
Myers AK et al. Psychoneuroendocrinology, 38:2810-4, 2013

**DIABETES AND SUICIDE**

Factors that influence suicidality in DM:

- male gender
- lower education level
- poor glycemic control
- depressive cognition
- severity of childhood abuse
- history of alcohol abuse
- past history of suicide attempt
- family history of completed suicide
- exacerbation of the diabetes and its complications

DIABETES AND SUICIDE

Methods of suicide attempt in patients with DM includes:

- high doses of insulin
- Metformin and other oral medications used in treatment of DM (glipizide, gliclazide, liraglutide, phenformin, sitagliptin)
- sugary substances
- psychotropics - antidepressant, antipsychotics


DIABETES AND SUICIDE

S - male Sex
A - older Age
D - depression
P - previous attempt
E - ethanol abuse
R - rational thinking loss (hopelessness)
S - lack of Social Support
O - organized plan
N - no spouse

Sickness - presence of medical illness


DIABETES AND PSYCHOTIC DISORDERS

A link between schizophrenia and DM has been known for over a century, long before the use of antipsychotic medications.

Studies before 1951 reported prevalence rates of diabetes in patients with psychotic disorders ranging from two to four times more than the healthy subjects.

The studies from the current era of pharmacotherapy show that DM is highly prevalent in people with psychotic disorders, including schizophrenia and schizoaffective disorders.

Diethelm O. Arch Neurol Psychiatry, 36:342-360, 1936
DIABETES AND PSYCHOTIC DISORDERS

The prevalence of DM in patients with psychotic disorders exceeds that in the general population:
- odds estimated to be between two and five times higher
- documented prevalence in those with psychosis of about 13%

Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)
- 11% of patients have been diagnosed with DM
- more than 25% of patients had fasting glucose levels >100 mg/dl


DIABETES AND PSYCHOTIC DISORDERS

Prevalence of DM in individuals with psychotic disorders is increasing over time:
- 6% in 1988 to more than 17% in 2002
- 1996 to 2001 - prevalence of diabetes in individuals with schizophrenia increased by 0.7 per year
- 6.9% in 1997 to 14.5% in 2004
- CDC - 2.5% in 1980 to 6.9% in 2011


DIABETES AND PSYCHOTIC DISORDERS

Traditional risk factors
1. Obesity
   - estimated relative risk of 1.5 - 2 in patients with schizophrenia
   - by age 25 years, people with psychosis have higher body-mass index than healthy individuals
   - patients with first-episode, drug-naive patients with schizophrenia, have a higher level of intra-abdominal fat than age-and BMI-matched healthy controls

De Hert M et al. World Psychiatry, 10:52-77, 2011
DIABETES AND PSYCHOTIC DISORDERS

Traditional risk factors
2. Adverse health behaviors
   - patients with psychosis consume fewer servings of fruits and vegetables daily, eat a diet higher in fat and lower in fiber than the general population and consume a higher amount of fast food
   - patients with schizophrenia spend a lot of time home, watching television on a daily basis and they do not engage in regular exercise


DIABETES AND PSYCHOTIC DISORDERS

Risk factors unique to psychotic disorders
1. People with schizophrenia (with and without treatment with antipsychotics) have increased risk of developing DM.
2. DM is associated with longer duration of psychotic disease.
3. Patients with severe psychotic illness are more likely to have DM than those with less severe psychotic illness.
4. Antipsychotic medications

Rouillon F et al. Eur Psychiatry, 20, supp 4, S345–S348, 2005

DIABETES AND BIPOLAR DISORDER

Patients with Bipolar Disorder have up to three times increased risk of DM relative to the general population.
10% of individuals with Bipolar Disorder had clear evidence of DM.

DIABETES AND ANXIETY DISORDERS

2006 Behavioral Risk Factors Surveillance System (BRFSS)
- the prevalence of lifetime diagnosis of anxiety was 19.5% in people with DM compared with 10.9% in patients without DM.

2012 Epidemiologic Catchment Area study
- anxiety disorders are not associated with increased risk of DM or risk of diabetes complications among those who have DM.

Increased anxiety symptoms in people with DM are associated with:
- increased diabetes symptoms burden
- less adherence with diabetes self-care recommendations
- physically inactive and smoking
- increased diabetes complications
- increased pain
- worsened blood glucose levels
- reduced quality of life
- increased depression
- increased body-mass index (BMI)
- greater disability

Needle and injection phobia and phobia of hypoglycemic episodes are 2 conditions associated with DM.

Anxiety symptoms overlap with the symptoms of hypoglycemic episodes (such as sweating, tremor, tachycardia), making it difficult for the person with DM to differentiate between feelings of anxiety and symptoms of low blood glucose that require immediate treatment.
DIABETES AND EATING DISORDERS

11.5-27.5% of adolescents with type 1 diabetes meet criteria for Eating disorder
- Bulimia Nervosa and Binge-eating Disorders are the most prevalent disorders

The prevalence of Eating disorders as comorbidities of type 2 diabetes ranges from 2.5% to 40%
- Binge-eating Disorders is most common Eating disorder, with a prevalence of 2.5-25.6%


DIABETES AND EATING DISORDERS

The comorbidity between DM and eating disorders is associated with:
- poorer glycemic control
- higher rates of hospitalization
- greater risks of microvascular complications, especially retinopathy and neuropathy
- increase in mortality
- poor response to standard eating disorder treatment

Custal N et al. BMC Psychiatry, 14: 140, 2014

PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

1. Mental illness and DM present as independent conditions
2. The course of DM can be complicated by emergence of psychiatric disorders
3. Psychiatric disorders act as independent risk factors for development of DM
4. Behavioral factors associated with mental illness may increase the risk for DM
5. Treatment with psychotropics increases the risk for DM
PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

Potential mechanisms linking mental illnesses and DM:
- genetic
- biological
- neuroendocrine
- environmental factors
- psychotropic medications

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Figure 1. The mechanisms that explain the association between severe mental illness and type 2 diabetes mellitus

Genetic factors
At least 37 common genes have been identified as risk genes for both DM and schizophrenia (GSK3, AKT1, DRD2, DISC1).
50% of patients with schizophrenia have positive family histories of DM compared with 4.6% of healthy control subjects.
A genetic component was suggested as candidate in the etiologies of both Bipolar Disorder and DM.

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PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

Biological factors

Altered immune function and chronic inflammation might result from stress and evidence suggests that these changes might be a precursor to both DM and psychiatric disorders.

Proinflammatory cytokines have been postulated to play a part in the development of insulin resistance and type 2 diabetes.

Inflammation and dysfunction of the immune system have been described in patients with Schizophrenia, MDD and Bipolar Disorder that might increase insulin resistance and predispose them to develop DM.

Schizophrenia
- interleukin-1β, interleukin-6, and transforming growth factor β, interleukin-12, interferon γ, tumor necrosis factor-TNFα, soluble interleukin 2 receptor
- raised concentrations of C-reactive protein (CRP) are associated with worse clinical symptoms of schizophrenia

Depression
- C-reactive protein (CRP) and pro-inflammatory cytokines, interleukin-6, interleukin-1, tumor necrosis factor-TNFα and interferon

Bipolar Disorder
- C-reactive protein, IL-1 receptor antagonist, soluble IL-6 receptor and T-lymphocyte activation
- Glycogen synthase kinase-3 (GSK-3) dysregulation may be relevant to the pathophysiology of both Bipolar Disorder and DM
- abnormalities in phospholipid metabolism have been described in both Bipolar disorder and DM
- mitochondrial dysfunction was found in both DM and Bipolar Disorder

References

PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

Neuroendocrine factors

- dysfunction of the hypothalamic–pituitary–adrenal axis, with increased cortisol secretion, associated with insulin resistance and metabolic syndrome
- reduced concentrations of insulin-like growth factor 1 and low levels of sex steroids
- activation of the sympathetic nervous system, resulting in increased concentrations of serum adrenaline and noradrenaline
- decreased plasma brain-derived neurotrophic factor (BDNF)

Brenner K et al. Psychoneuroendocrinology, vol. 34, no. 6, pp. 859–868, 2009
Kreitl K et al. Diabetes Obes Metab. 12:430–36, 2010

PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

Environmental factors

Early life

- intrauterine disturbances during gestation may contribute to the risk of DM and mental illnesses
- prenatal infections and maternal immune changes
- fetal overexposure to cortisol secondary to maternal stress
- childhood adversity

St Clair D et al. JAMA 294, 557–562, 2005

PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

Adult lifestyle

- people with mental illness are more likely than the general population to be sedentary, eat diets that are rich in saturated fats and refined sugars while avoiding fruit and vegetables
- factors that may contribute to poor access to healthy lifestyle choices in individuals with mental illnesses are neighborhood environment, lower socioeconomic status and educational level and social isolation

PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

- Two-thirds of people with schizophrenia are vitamin D deficient and twofold more likely to have schizophrenia than those with vitamin D sufficiency.
- Low level of vitamin D during childhood may be associated with schizophrenia.
- Gestational Zn deficiency
- The lifetime prevalence rates of alcohol, smoking, and substance use disorders are significantly elevated in patients with mental disorders.


MRI scanning
- Prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in DM are higher than in healthy control subjects, and correlate with mild depressive symptoms.
- Hippocampal atrophy in DM associated with mood symptoms and cognitive decline.
- White matter lesions have found to be associated with Bipolar Disorder.

Lyoo IK et al. Arch Gen Psychiatry, 66:878–879, 2009

Antipsychotics
- Observations studies indicate that antipsychotic treatment is associated with a higher prevalence of DM than no treatment.
- Untreated patients have a prevalence of DM of 2.1% comparing with those taking antipsychotic medication which have a prevalence of 12.8%.
- Increased prevalence of DM in patients with schizophrenia was found in patients treated with both typical and atypical antipsychotics. Among the typical antipsychotic, increased prevalence is associated with both low-potency and high-potency agents.

Second-generation or atypical antipsychotic has three times the rate of new onset metabolic syndrome compared to first generation or typical or conventional antipsychotic.

- Olanzapine and Clozapine - greatest effects on DM
- Aripiprazole and Ziprasidone - smallest effects on DM

The degree of weight gain varies considerably between the different antipsychotics.

CATIE trial:
- individuals who experienced the greatest amount of weight gain and the greatest percentage (7% or more) of their total bodyweight were those taking Olanzapine

RCTs:
- Clozapine and Olanzapine - the highest weight gain
- Quetiapine and Risperidone - intermediate risk of weight gain
- with the exception of Aripiprazole and Ziprasidone, all antipsychotics induce weight gain with long-term use
PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

Antipsychotics can directly cause DM through the effect on muscarinic, dopaminergic, histaminic and serotonergic receptor:

1. M3 receptor has been closely linked to diabetic side effects of antipsychotics
2. Dopaminergic hypofunction might lead to overeating and resulting weight gain
3. H1-histamine antagonism
4. 5-HT receptors antagonism


Other proposed mechanisms to explain the risk of DM associated with antipsychotics:

- Glucose metabolism dysregulation
- Leptin and ghrelin
- Oxidative stress


Antidepressants

Several factors were reported to support the association between antidepressant use and the risk of new-onset DM:

- Dysfunction of the hypothalamic-pituitary-adrenal axis
- Increase in the serotonin transmission
- Weight gain through high affinity to serotonergic, histaminergic, cholinergic and dopaminergic receptors
PHYSIOPATHOLOGY OF THE COMORBIDITY OF DIABETES AND PSYCHIATRIC CONDITIONS

Table 4: Propensity of psychotropics to cause weight gain and impairment of glycemia control

Antidepressants that cause weight gain:
- TCAs, MAOI, Mirtazapine and some SSRI's (Paxil, Fluvoxamine)

Antidepressants that are weight neutral:
- Venlafaxine (SNRI), some SSRIs (Fluoxetine)

Antidepressants that induce weight loss:
- Wellbutrin-NDRI

Mood stabilizers
- Lithium and Sodium Valproate are associated with weight gain and impaired glycemia control
- Carbamazepine - intermediate risk for gain weight

IMPLICATIONS FOR PATIENT’S CARE

- 45% of the cases of mental disorder and severe psychological distress go undetected among patients treated for DM
- 70% of cases of DM in people with mental illnesses are estimated to be undiagnosed (vs. 25-30% in the general population)
- CATIE study - 38% of patients with Schizophrenia and DM were not receiving any treatment for DM

Li C et al. Diabetes Care, 33:1061-64, 2010

IMPLICATIONS FOR PATIENT’S CARE

- Primary care is the sole form of health care used by more than one third of patients receiving care for a mental health condition.
- The most effective approach in treating the mental disorders and medical comorbidities is the use of a collaborative care in which mental health is integrated into primary care.

Russell L. October Mental Health Care Services in Primary Care: Tackling the Issues in the Context of Health Care Reform. Washington, DC: Center for American Progress, 2010

IMPLICATIONS FOR PATIENT’S CARE

Professionals barriers:
- lack of clarity about whose responsibility screening is
- lack of awareness of recommendations for screening and follow-up monitoring:
  - FDA (US Food and Drug Administration)
  - ADA (American Diabetes Association)
  - APA (American Psychiatric Association)
  - AACE (American Association of Clinical Endocrinologists)
- level of comfort of the primary care providers to treat patients with mental illness
- level of knowledge or expertise of the psychiatrists to provide medical care for their patients

Lord Old et al. Gen Hosp Psychiatry, 32:519-543, 2010
IMPLICATIONS FOR PATIENT’S CARE

American Diabetes Association standards of care
- “People with diabetes should receive medical care from a team that may include physicians, nurse practitioners, physician’s assistants, nurses, dietitians, pharmacists and mental health professionals with expertise in diabetes…”
- “Routinely screen for psychosocial problems such as depression and diabetes-related distress, anxiety, eating disorders, and cognitive impairment.”