Antipsychotics and glucose metabolism: assessing the risks

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Diabetes mellitus

- A group of metabolic diseases
- Characterised by hyperglycaemia due to defects in insulin secretion, action, or both
- Primary insulin actions occur at
  - skeletal muscle (stimulation of glucose disposal)
  - liver (inhibition of glucose production)
  - adipose tissue (inhibition of lipolysis)
Primary effects of insulin on blood glucose

- **PANCREAS**
  - INSULIN
  - Decrease hepatic glucose production
  - INSULIN
  - Increase peripheral glucose uptake

- **LIVER**
- **MUSCLE**
Type 2 diabetes mellitus

- Disturbances in insulin action lead to abnormalities in glucose and lipid metabolism

- Type 2 is the most prevalent form, resulting from insulin resistance plus an insulin secretory defect

- A serious public health problem with over $100 billion in annual expenditure in the US

Risk factors for diabetes mellitus

- Abdominal adiposity (fat)
- Increasing age
- Pregnancy (gestational diabetes)
- Ethnicity
- Gender?
- Major psychiatric illnesses
- Medications, including antipsychotics
Diabetes mellitus and gender

- Women have been reported to have increased risk for diabetes, compared to men
- However, increased risk is related to decreased fitness and increased adiposity
- When women and men are matched for fitness and adiposity, women are reported to have equal or lower risk for diabetes
Diabetes risk related to baseline BMI, gender and race

Prevalence of diabetes and impaired fasting glucose (IFG)

Neuropsychiatric conditions and glucose regulation

Associations between disturbances in glucose regulation and disease/Severity

- Depression
- Bipolar disorder
- Alzheimer’s disease
- Schizophrenia
Glucoregulatory abnormalities and diabetes in schizophrenia

- Abnormalities in peripheral glucose regulation and type 2 diabetes can occur more commonly in individuals with schizophrenia than in the general population.

- Although first reported prior to the introduction of antipsychotic medications\(^1\), antipsychotics can contribute significantly to abnormalities in glucose regulation.

\(^1\)Braceland et al, 1945.
Conventional antipsychotics: effects on glucose regulation and diabetes

- Aggravation of existing diabetes\(^1\)
- New-onset type 2 diabetes\(^2\)
  - introduction of chlorpromazine increased prevalence from 4.2\% to 17.2\%\(^3\)
- Abnormal glucose regulation\(^4\)
- Association not always found for all drugs\(^5\)

Clozapine and olanzapine: effects on glucose regulation and diabetes

- Abnormal glucose regulation, exacerbation of existing type 2 diabetes, new-onset type 2 diabetes and diabetic ketoacidosis (DKA)
  - Clozapine
    Estimated type 2 incidence: 12–36%
  - Olanzapine
    Estimated type 2 incidence: (3.1% ³) 6–~30%

- Effects reported with and without weight gain

Olanzapine database review

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=445</th>
<th>Olanzapine n=4577</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of 160mg/dL&lt;RG&lt;200mg/dL*</td>
<td>1.57%</td>
<td>2.04%</td>
</tr>
<tr>
<td>Incidence of RG≥200mg/dL*</td>
<td>0.89%</td>
<td>1.05%</td>
</tr>
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</table>

- 25% more hyperglycaemia on olanzapine than on placebo, but actual incidence is hard to interpret

- Problems:
  - Calculation using ad hoc criteria and RG rather than FBG or OGTT
  - RG≥160mg/dl may not be sensitive enough; risk of under-diagnosis
  - Real-world samples using ADA criteria yield higher numbers (e.g. 18%)

*Definite/possible/transient: Definite = clear patterns of elevated RGs greater than threshold values, starting during trial and sustained until end of trial; Possible = clear elevations only at the end of trial period and not earlier; Transient = clear elevations during but resolved by the end of the trial period.

1Shiigi Y et al. ACNP 1999:202 (abstract).
Quetiapine and risperidone: effects on glucose regulation and diabetes

• Limited observations for quetiapine

• Fewer observations linking risperidone with impaired glucose regulation or diabetes (e.g. in HIV+ male with DKA)
  - suggests a less frequent or smaller effect
  - risperidone reportedly used without complications in patients with comorbid diabetes

<table>
<thead>
<tr>
<th>Lab test</th>
<th>Ziprasidone</th>
<th>Placebo</th>
<th>Haloperidol</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n (%)</td>
<td>n</td>
<td>n (%)</td>
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<tr>
<td>Random glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.2xULN</td>
<td>2362</td>
<td>352</td>
<td>393</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>(14.9)</td>
<td>(12.2)</td>
<td>(16.3)</td>
<td>(14.9)</td>
</tr>
</tbody>
</table>
Diabetic ketoacidosis

● Characterised by:
  – hyperglycaemia: glucose usually >300mg/dL
  – ketonaemia: total serum ketones >3mM
  – acidosis: blood pH <7.3 or HCO₃ <15mmol/L
  – mortality rate generally 2–10%, can be higher

● Clinical symptoms
  – polyuria
  – nausea or vomiting
  – shortness of breath
  – fever
  – polydipsia
  – abdominal pain
  – CNS depression
  – infection
Effects of antipsychotics on glucose regulation and diabetes: summary

- For all agents, small increases in glucose levels are more common than large increases, but more quantitative data needed.

- Long-term adverse cardiovascular effects of small increases in glucose levels below ‘impaired’/diabetic thresholds are well-established in various populations.
Complications of hyperglycaemia include microvascular disease

- Retinopathy with potential loss of vision
- Nephropathy leading to renal failure
- Peripheral neuropathy with risk of foot ulcers, amputation, and Charcot joints
- Autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction

Complications of hyperglycaemia

- Hyperglycemia can also cause or contribute to macrovascular disease (i.e. atherosclerosis)
  - cardiovascular disease
  - peripheral vascular disease
  - cerebrovascular disease

- Insulin resistance syndrome
  - increased incidence of hypertension, dyslipidaemia, and obesity

Hyperglycaemia: impaired glucose regulation to diabetes mellitus

<table>
<thead>
<tr>
<th>Stages</th>
<th>Normoglycaemia</th>
<th>Hyperglycaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose regulation</td>
<td>Impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)</td>
<td>Diabetes mellitus Not insulin requiring for control Insulin requiring for survival</td>
</tr>
</tbody>
</table>

Type 1
Type 2
Other specific types

Macrovascular disease risk (e.g. myocardial infarct and stroke) increases continuously with increasing glucose levels
– no clear threshold

Progressive relationship between glucose levels and increased cardiovascular risk observed in non-diabetic\(^1\) and diabetic persons\(^2\)

Odds ratio of MI as a function of fasting blood glucose

Fasting glucose (mmol/L) quartile

<81mg/dL  81–94mg/dL  94–114mg/dL  >114mg/dL

Carotid intima-media thickness as a function of FPG

Schizophrenia-related abnormalities in glucose regulation

Mean plasma glucose (mg/dL±SE) and insulin (mU/mL±SE) before and after 50g oral dextrose in patients with schizophrenia (n=10) and bipolar affective disorder (n=10), and normal healthy controls (n=10)

Medication-related abnormalities in glucose regulation in schizophrenia

Oral 50g dextrose challenge in patients with schizophrenia (n=48) and healthy controls (n=31), with treatment groups matched for age and body mass index (BMI).

*Significant effect of treatment condition, p<0.05

HOMA insulin resistance in treated patients with schizophrenia

IVGTT with MinMod Analysis: antipsychotic-associated differences in insulin sensitivity

Insulin resistance in treated patients with schizophrenia

Newcomer JW et al, unpublished data.
Cardiovascular mortality in schizophrenia

- Increased in some, but not all, earlier studies
- Cardiovascular disease takes years (e.g. some pre-antipsychotic) and involves multiple factors (e.g. dyslipidemia, smoking, obesity)
- Danish Psychiatric Case Registry (1970–1987; n = 9,156 with schizophrenia, n = 1,081 with death and cause) indicates standardised mortality rates increased for combined cardiovascular and cerebrovascular disease in both men (3.33 higher than control) and women (2.42 higher than control) with schizophrenia¹

Risks hypothesised to be associated with abnormal glucose regulation

- TD severity or risk may increase with increasing glucose dysregulation
  
  - Glucose dysregulation and comorbid diabetes associated with worse clinical status
  
  - Altering glucose or insulin levels can alter cognitive performance

Abnormal movements and glucose and insulin plasma levels in treated schizophrenia

Eight of 21 patients met criteria for IGT, none for diabetes

AIMS = Abnormal Involuntary Movement Scale


(r=−0.48, df=16, p <0.04)
Antipsychotic-induced weight gain

- Complications of obesity include hyperglycaemia and type 2 diabetes (insulin resistance), hypertension, cardiovascular disease, and dyslipidaemias.

- Complications of obesity can add to risk for cardiovascular disease (variable BMI threshold).

- First reported as an effect of conventional agents, some atypical antipsychotic agents can induce significant weight gain, e.g. clozapine and olanzapine.

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Weight change after 10 weeks on standard drug doses, estimated from a random effects model

- Placebo
- Conventional antipsychotic
- Novel antipsychotics
- Non-pharmacological controls

Diabetes screening criteria (1)

- Testing is considered for everyone \( \geq 45 \) years
  - if normal, repeat at 3-year intervals

- Testing is considered at a younger age or done more frequently in individuals who
  - are obese \(( \geq 120\% \) ideal weight or \( \text{BMI} > 27 \text{kg/m}^2 \))
  - have first-degree relative with diabetes
  - are members of a high-risk ethnic population (e.g. African American, Hispanic American, Native American, Asian American, Pacific Islander)
Diabetes screening criteria (2)

- Have delivered a baby weighing >9lb or have been diagnosed with gestational diabetes
- Are hypertensive (≥140/90)
- Have a high-density lipoprotein cholesterol level ≤35mg/dL and/or a triglyceride level ≥250mg/dL
- Had IGT or IFG on previous testing

(FBG testing preferred over OGTT because of ease of administration, convenience, acceptability and cost)
Recommendations: risk level determines level of monitoring

- Previous history of DKA
- Previous diagnosis of diabetes mellitus
- General risk factors: schizophrenia; medications; depression; Alzheimer’s; ADA risk criteria
Recommendations: monitoring for hyperglycaemia in schizophrenia

- Annual maintenance screen (e.g. FPG)
- Screen high risk patients more frequently and carefully (e.g. OGTT)
- Baseline measurement prior to new treatment
- Serial measurement during treatment initiation and dose titration (frequency determined by level of risk)
  - FPG – more convenient
  - OGTT – more sensitive
Conclusions (1)

- Antipsychotic treatment in schizophrenia is associated with changes in glucose regulation, potentially interacting with a disease-related abnormality in glucose regulation.

- Could lead to acute and long-term complications, including increased risk for DKA and cardiovascular events (e.g. MI and stroke).
Conclusions (2)

- Treatment-associated changes in glucose regulation may interact with treatment-induced weight gain to further disturb glucose regulation.

- Treatment-associated changes in glucose regulation may interact with treatment-associated changes in triglyceride levels and treatment-induced weight gain to further increase risk for cardiovascular disease.
Conclusions (3)

- Patients taking antipsychotics should undergo regular monitoring for hyperglycaemia, dyslipidaemia and weight gain

- Education, in addition to monitoring, will be required to reduce the risk of diabetic ketoacidosis

- Collaboration between the psychiatrist and either an endocrinologist, internist or interested family practice physician is required
Conclusions (4)

- Clinicians should individualise treatment decisions:
  - consider potential antipsychotic medication effects on glucose regulation and weight in the context of any pre-existing risk factors (obesity, smoking, hypertension, race/ethnicity, family history, or pre-existing hyperglycaemia)

- Future research is needed to guide treatment decisions and optimise long-term outcomes