Thyroid Function and Diabetes Mellitus, Are They Important to Psychiatry?
Friday, Oct. 26, 2012

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Disclosures

I have received honoraria and consultation fees from Abbott (Synthroid®) and Genzyme (Thyrogen®)
Case history #1

- Mr. H.S., an 81 yo male, is referred for a depressed affect, memory dysfunction, episodes of anxiety and poor sleep.
- He does not have a family history of thyroid disorders and does not present a goiter on neck palpation.
- Thyroid profile:
  - date 1 date 2
  - Jan 2010 mar 2010
  - TSH(0.45 - 4.50 mU/L) 7.2 7.3
  - fT4 (9 - 25 pmol/L) 18 16
  - TPO antibody negative negative

- Would you treat this individual with levothyroxine replacement?
Program

1. Thyroid physiology
Hypothalamic-pituitary-thyroid Axis

Martin Surks, Rubens Sievert. NEJM. 1995; 333:1688-1694
Montefiore Med Ctr
Program

1. Thyroid physiology
2. TSH reference ranges
Serum TSH in the screening for thyroid disease

![Graph showing TSH levels with hyper, euthyroid, and hypo labels.](image)

- **Euthyroid** range: 0.005 to 0.5 mU/L
- **Hyper** range: 0.5 to 5.0 mU/L
- **Hypo** range: 5.0 to 500 mU/L

TSH-T4 interrelations

- TSH (mU/L) on the Y-axis
- FT₄ (ng/dL) on the X-axis
- Normal TSH range
- Undetectable values

Legend:
- Hypothyroid
- Euthyroid
- Hyperthyroid

Points:
- A
- B
- C
- D
Reported differences in the TSH (upper 97.5% reference limit)

Figure 3. Reported differences in the TSH upper (97.5%) reference limit

- AACE guidelines
- Endocrine Society
  2nd/3rd trimester pregnancy
  3.0
- German Ship study
  2.1
- Mexican Americans
  50-59 year old
  USA
  NHANES
  3.9/4.0
- 2.5
  1st trimester pregnancy
  Endocrine Society
- 4.2
  USA
  NHANES
  Caucasians
- 3.6
  USA NHANES
  20-29 year olds
- African Americans
- 7.5
  USA NHANES
  > 80 year old
- 13% of this cohort
- 20.0
  In-hospital patients

Surks MI and Hollowell JG. NHANES III. JCEM 2007; 92: 4575 -4582.
Program

1. Thyroid physiology
2. TSH reference ranges
3. Solid diagnosis of subclinical hypothyroidism
Subclinical hypothyroidism.
Prevalence in women.

Thyroid Peroxidase Antibodies

**Figure 1.** Box and Whisker plots of TSH values grouped according to increasing TPO antibody levels (TPO-Ab) in 759 euthyroid female relatives of patients with documented AITD, showing a positive correlation coefficient 0.386, \(P < 0.001\). Reproduced from Strieder et al (2003, *Clinical Endocrinology* 59: 396–401) with permission.\textsuperscript{12}
Program

1. Thyroid physiology
2. TSH reference ranges
3. Solid diagnosis of subclinical hypothyroidism
4. Extrinsic Hypothalamic-pituitary-thyroid axis regulators
The feed-back mechanism and role of hypothalamus.

- Glucocorticoids
- Dopamine
- Somatostatin
- Reduced leptin
- Cytokines (TNF-α)
- NFκB-induced D2 expression in HYPO
- Bile acids
- Smoking

1. Thyroid physiology
2. TSH reference ranges
3. Solid diagnosis of subclinical hypothyroidism
4. Extrinsic HPT axis regulators
5. Thyroid hormone regional targets in the brain
Neurogenesis of the Hippocampus

Cerebral $T_3$ autoregulation

Theo J Visser. Erasmus Univ. Medical Center Rotterdam, Netherlands
Overt hypothyroidism and brain function in the adult.

- Increased rates of *depression and anxiety* in cross-sectional studies.
- Decreased *cognitive function* in cross-sectional studies, particularly memory.
- *Affect* and *cognitive function* improve with L-T4 therapy, but may not completely reverse.
- Reports of *cerebellar ataxia* associated with hypothyroidism that improved with levothyroxine have appeared in the literature.
1. Thyroid physiology
2. TSH reference ranges
3. Solid diagnosis of subclinical hypothyroidism
4. Extrinsic HPT axis regulators
5. Thyroid hormone regional targets in the brain
6. Clinical evidence for the association of subclinical hypothyroidism and affective disorders and cognitive dysfunction
Brain Glucose Metabolism in Hypothyroidism: A PET Study before and after Thyroid Hormone Replacement Therapy

Subclinical hypothyroidism and brain function in the adult.

• Some (but not all) studies show increased rates of depression, anxiety, or cognitive dysfunction, with improvement after L-T4 treatment (results may depend on cognitive domain studied).

• Recent large cross-sectional studies showed no clinically relevant correlations between TSH or thyroid hormone levels and depression, anxiety, or cognitive screen.

• Three recent randomized, placebo-controlled, blinded studies of L-T4 treatment in mild SCH and brain outcomes have been inconsistent.

• It is possible that most divergences in the results may be a consequence of different methodologies, specifically:
  – differences in the age of the populations studied,
  – sample composition,
  – differing degrees of severity of SCH,
  – inclusion and exclusion criteria,
  – standardization of evaluation instruments.

• Effects of subclinical thyroid disorders cannot be extrapolated over different age groups.
Program

1. Thyroid physiology
2. TSH reference ranges
3. Solid diagnosis of subclinical hypothyroidism
4. Extrinsic HPT axis regulators
5. Target cerebral regions
6. Clinical evidence for the association of subclinical hypothyroidism and affective disorders and cognitive dysfunction
7. Conclusion
Suggested Approach to Diagnosis and Management of Subclinical Hypothyroidism

- **Serum TSH > 4.5 mU/L**
  - Repeat serum TSH measurement with fT4 measurement in 2-12 weeks
  - **Serum TSH within the normal reference range 0.45 – 4.5 mU/L**
    - Monitor every 6-12 months for several years
  - **Serum TSH > 10 mU/L**
    - Treat with levothyroxine
  - **Serum TSH 4.5 – 10 mU/L**
    - FT4 level decreased
    - Pregnant or contemplating pregnancy

**Recommendation 31** - There is insufficient evidence to support using thyroid hormones to treat depression in euthyroid patients.
Treatment of Mild Thyroid Failure

• Starting dose may range from 12.5 ug/day to full replacement (1.0ug/kg/day).
  
  – One randomized control trial assigned T4 doses on the basis of the initial serum TSH values as follows: 25 μg for TSH 4.0 to 8.0 mIU/L, 50 μg for TSH 8 to 12 mIU/L, and 75 μg for TSH > 12 mIU/L. After two months only minimal further adjustments were required to achieve euthyroidism.

• Reassess TSH after 4-8 weeks.
• Euthyroid status may require 8 -16 weeks.
• May be pertinent to retest TFT’s after 6 month, as euthyroidism may accelerate metabolism of l-T4.
• Steps should be taken to avoid overtreatment with T4. This has been reported in 20% of those treated with thyroid hormone.
Case history # 2

• Mrs. CD a 44 yo obese woman is admitted to the ED for **symptomatic hyperglycemia** *(random blood sugar 27.2mmol/L)*.

• This patient was not a known diabetic but her mother was treated for type 2 dm.

• She was currently treated for hyperlipidemia and HTN with fenofibrate and amlodipine respectively.

• One month prior to this admission she was started on olanzapine by her psychiatrist for schizophrenia.

• After a brief hospitalization, she was d/c on metformin 500mg po tid and glyburide 2.5mg po at suppertime.

• The olanzapine was never stopped.

• Follow-up was arranged with her family md.
Program

- Is there a link between schizophrenia and type-2 diabetes mellitus?
- What factors form the basis of this association?
- What is the pathophysiologic mechanism of these risk factors?
- What is the impact of atypical antipsychotics on this risk of treatment-emergent type-2 diabetes?
- How should patients with schizophrenia at risk for incident type-2 dm be managed?
Although 21% of patients were identified as having dm-2 once they were actively screened, only 4.9% had previously received this diagnosis.
Risk Factors for Type-2 DM

- Age > 40 years.
- First degree relative with diabetes.
- Member of high-risk population (eg Aboriginal, Hispanic, south Asian, Asian, African descent).
- History of IGT or IFG.
- Presence of complications associated with DM.
- Vascular disease.
- History of GDM.
- History of delivery of a macrosomic infant.
- Hypertension.
- Dyslipidemia.
- Overweight.
- Abdominal obesity.
- Acanthosis nigricans
- **PCOS.**
- **Schizophrenia.**
- Turner’s syndrome.
- Others.

Canadian Diabetes Association. CMAJ. 2003
Program

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Metabolic Syndrome: Harmonized Definition

ANY 3 of these factors:

- Plasma triglycerides >1.7 mmol/l
- HDL cholesterol
  - Men <1.0 mmol/l
  - Women <1.3 mmol/l
- Blood pressure
  - >130 mmHg / ±>85 mmHg
- Serum glucose >5.6 mmol/L
- Central obesity
  - Europid
  - Men ≥102 cm
  - Women ≥88 cm

• WHEN PRESENT, 1.5-2.0 X FRAMINGHAM RISK SCORE


Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 120:1640–1645
Prevalence of diabetes, obesity, and metabolic syndrome in subjects with and without schizophrenia (CURES-104).

Possible Reasons for Increased Association Between Schizophrenia, Metabolic Syndrome and Type-2 Diabetes Mellitus

1. Common genetic vulnerabilities
   – Family History
2. Common environmental vulnerabilities
   – Low birth weight
3. Common Pathophysiologic Processes
   – Chronic stress activated hypothalamic-pituitary-adrenal axis.
4. Common behavioral & lifestyle factors
   – Sedentary
   – Diet
   – Obesity & Weight Gain
5. Contribution of antipsychotic medications
   – Typical antipsychotics
   – Atypical antipsychotics
Fat distribution in Schizophrenia

### Fat Distribution in Schizophrenia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Schizophrenia patients</th>
<th>Controls (BMI matched)</th>
<th>Post-treatment OLZ or RPD (6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI Kg/M2</td>
<td>24.6 +/- 0.7</td>
<td>29.4 +/- 0.8</td>
<td>23.0 +/- 0.4</td>
</tr>
<tr>
<td>IAF cm²*</td>
<td>38.0 +/- 4.8</td>
<td>131.7 +/- 20.7</td>
<td>116.8 +/- 20.2</td>
</tr>
<tr>
<td>Cortisol (RIA, 0830 hrs) nmol/L*</td>
<td>306.2 +/- 49.6</td>
<td>192.7 +/- 19.7</td>
<td>192.7 +/- 20.7</td>
</tr>
</tbody>
</table>

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Basal Over-activity of the Pituitary-adrenal Axis in Schizophrenia

Ryan MCM. Psychoneuroendocrinology. 2004;29:1065-1070
Is there a link between schizophrenia and type-2 diabetes mellitus?

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What is the pathophysiologic mechanism of these risk factors?

What is the impact of atypical antipsychotics on this risk of treatment-emergent type-2 dm?

How should patients with schizophrenia at risk for incident type-2 dm be managed?
Diabetes Among Patients with Schizophrenia — What is the Impact of Atypical Antipsychotics?

Patients with Schizophrenia

- Pre-atypicals (1991)
  - Age 45–64
  - 18.8%

- Post-atypicals (1999)
  - Age 40–59
  - Conventional: 9%
  - Atypical: 18.8%

General Population

- NHIS (1994)
  - Age 45–64
  - 6.3%

References:
Falls in Insulin Secretion and Insulin Sensitivity Lead to Progression From NGT to IGT to Diabetes

## Adverse metabolic changes occurring with atypical antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight Gain</th>
<th>Elevated Glucose Levels</th>
<th>Elevated Lipid Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

0, no risk or rarely causes adverse effects at therapeutic doses; +, mild or occasionally causes adverse effects at therapeutic doses; ++, sometimes causes adverse effects at therapeutic doses; +++ frequently causes adverse effects at therapeutic doses.
• Both genetic and environmental factors are contributing to this pronounced co-morbidity between schizophrenia and overweight.

• Among the latter, antipsychotic drugs and, especially, second generation antipsychotics (SGAs) play a pivotal role.

• Particularly, clozapine and olanzapine are associated with excessive weight gain (up to 2 kg per month), but also the metabolism of glucose and lipids is affected to a varying degree.
Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia: systematic evaluation

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personal/family history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*More frequent assessments may be warranted based on clinical status*


# How Should We Screen

<table>
<thead>
<tr>
<th>Test</th>
<th>Impaired Glucose Tolerance</th>
<th>Type-2 DM (mmol/L)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>oGGT</td>
<td>7.8 - 11.1 (mmol/L)</td>
<td>&gt;11.1 (mmol/L)</td>
<td>&gt;90%</td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>6.1 - 6.9 (mmol/L)</td>
<td>&gt;7.0 (mmol/L)</td>
<td>40</td>
<td>84 - 99</td>
</tr>
<tr>
<td>RPG</td>
<td>7.8 - 11.1 (mmol/L)</td>
<td>&gt;11.1 (mmol/L)</td>
<td>50</td>
<td>92 - 98</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.7 - 6.4%</td>
<td>≥6.5%</td>
<td>31</td>
<td>79 - 100</td>
</tr>
</tbody>
</table>
Is there a link between schizophrenia and type-2 diabetes mellitus?

What factors form the basis of this association?

What is the pathophysiologic mechanism of these risk factors?

What is the impact of atypical antipsychotics on this risk of incident type-2 dm?

How should patients with schizophrenia at risk for incident type-2 dm be managed?
Current interventions against antipsychotic-induced weight gain

• Current interventions against antipsychotic-induced weight gain fall into three categories.

1. The first category involves changing antipsychotic medication to a compound less prone to result in weight gain. This strategy is recommended in clinical guidelines and results in a modest slowing of antipsychotic-induced weight gain to approximately 1.9 kg. Change of medication, however, may increase the risk of exacerbating psychotic symptoms.

2. The second category involves lifestyle intervention and/or cognitive therapy and appears to slowdown the SGA-induced weight gain by 2.6 kg after 3 to 4 months; 4.2 kg after 6 months; and 3.1 kg after 12 to 18 months of treatment.

3. Finally, adjuvant medical treatment, the third category, has been attempted with numerous drugs. Metformin is by far the most investigated of these drugs and is associated with the most pronounced deceleration of antipsychotic-induced weight gain: 2.9 kg over 13 weeks compared with placebo. Current data converge towards adjunctive treatment with GLP-1 analogs as a potentially new avenue in the prevention and treatment of schizophrenia patients with antipsychotic-induced weight gain.
Conclusions

• Screening is essential as patients fulfill criteria for “high-risk individuals”.

• There is no ideal screening measure, however the ADA-suggested metabolic panel is useful.

• GPs/psychiatrists should screen and monitor.

• Simple lifestyle interventions, avoidance of dysmetabolic atypical antipsychotics and antidiabetic medications may be effective in preventing type-2 diabetes onset in high-risk patients.