Psychological Factors And The Pathophysiology of Type 2 Diabetes: A 30 Year Perspective

Richard S. Surwit

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Type 2 Diabetes: A Progressive Disease

- Normal
- IGT
- Prediabetes state: 57,000,000
- Type 2 Diabetes
- Clinical disease: 24,500,000
- Complications
- Disability Death

Diabetes Complications

**Macrovascular**
- Cerebrovascular disease
- Heart disease and hypertension
- Erectile dysfunction
- Peripheral vascular disease

**Microvascular**
- Diabetic eye disease (retinopathy, cataracts, macular edema)
- Autonomic Neuropathy
- Renal disease
- Peripheral Neuropathy
- Foot problems
Relationship Between BMI and Risk of Type 2 Diabetes


Stress is also a factor: Stress increases the incidence of Type 2 Diabetes over 35 years

C57BL6J Ob/Ob Mouse
<table>
<thead>
<tr>
<th></th>
<th>CONTROL</th>
<th>STRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean n=12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ob/ob n=8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lean n=9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ob/ob n=6</td>
<td></td>
<td></td>
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</tbody>
</table>

Plasma Glucose (mg/dl)

Plasma Insulin (µu/ml)

Surwit et al. *Diabetes* 1984:33, 616-618
Pima Indians
Stress Test Times

Minutes post prandial

Serum glucose (mM)

Caucasian

Pima

“But if the depraved and degenerate nervous liquor doth continually flow into the blood, it produces sometimes the bloody dysentery and sometimes the diabetes...”

• What was Willis’s “Nervous Liquor”?
  – Animal and human research provides some clues
Again mice helped provide the answer
Epinephrine Interacts with Obesity to Determine Glucose in Mice

Dose is micrograms/10 g body weight.

Is Hyperglycemia Due to the Interaction of Visceral Fat and Epinephrine?

Normal

Type 2 diabetes

Courtesy of Wilfred Y. Fujimoto, MD.
To test this hypothesis, we measured trunk fat with a DEXA scan as well as plasma epinephrine in 60 African American women.

Standard regions of a DEXA scan:
1. head
2. trunk (central)
3. right arm
4. left arm
5. right leg
6. left leg
Association between % Trunk Fat and Fasting Glucose in African American Women

Surwit et al. 2010, *Obesity*
Association Between Plasma EPI Levels and Fasting Glucose in African American Women with Low Central Adiposity

R Sq Linear = 6.57E-4

Surwit et al. 2010, *Obesity*
Association Between Plasma EPI Levels and Fasting Glucose in African American Women with High Central Adiposity

Surwit et al. 2010, *Obesity*
Fasting Glucose Levels by Trunk Fat Group (Low/High) and EPI Group (Low/High) in African American Women

Surwit et al. 2010, *Obesity*
Epinephrine Interacts with Central Adiposity in Producing Elevated Fasting Glucose
Cumulative Diabetes Incidence by Category of Normal Fasting Plasma Glucose

Only 30% of Obese People Develop Diabetes.
Do Epinephrine Levels Compensate for Obesity to Maintain Normal Glucose Levels In Most People?
Method

We examined 445 healthy non-diabetic individuals (159 white women, 156 white men, 75 AA women and 55 AA men) who had completed a DEXA scan as well as collection of both plasma and urine epinephrine measurements.
Plasma Epinephrine Levels In Men and Women With Fasting Glucose <95 mg/dl

Georgiades et al, in preparation
Urinary Epinephrine Levels in Men and Women With Fasting Glucose < 95 mg/dl

Georgiades et al, in preparation
Other Studies Have Found Similar Results

<table>
<thead>
<tr>
<th>BMI</th>
<th>16-20</th>
<th>21-23</th>
<th>24-25</th>
<th>26-28</th>
<th>28-38</th>
<th>N=577</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary EPI (nm/dl)</td>
<td>72</td>
<td>67</td>
<td>53</td>
<td>62</td>
<td>41</td>
<td>P&lt;.001</td>
</tr>
</tbody>
</table>

Chinese men Lee et al, 2001, *Metabolism*


However, Epinephrine Does Not Decrease With Increasing Trunk In Individuals with Fasting Glucose > 95 mg/dl

Georgiades et al, in preparation
Potential Mechanisms By Which Non-Diabetic Individuals Compensate for Increased Obesity

Glucose → CNS → Adrenal Medulla

CNS

FFAs

Liver → Vagus?

FFAs? → Leptin?

Adipose Tissue
Personality Factors Have Also Been Related to Glucose Metabolism and Obesity

• Hostility is a personality construct that has been associated with increased risk of cardiovascular disease and all cause mortality.
A Relationship of Hostility to Fasting Glucose Has Been Repeatedly Found in African American Women

<table>
<thead>
<tr>
<th></th>
<th>Study A</th>
<th>Replication Study B</th>
<th>Replication Study C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>.22*</td>
<td>.34*</td>
<td>.34*</td>
</tr>
</tbody>
</table>

*p<.04

Georgiades, et al, 2009 *Psychosomatic Medicine*
How Does Hostility Impact Glucose Metabolism?

• Determine the variables which may mediate Hostility’s impact glucose metabolism in these populations
  – Sympathoadrenal activity
  – BMI
• Determine the relationship between Hostility and glucose kinetics in healthy White and African American men and women

Surwit et al, 2009, *Psychosomatic Med*
The Labeled IVGTT

- Enables modeling of glucose kinetics in vivo using the “minimal model”
Method: The IV GTT

- 115 African American and White male and female volunteers
- Hostility measured by the CMHOST
- Glucose bolus (300mg/kg) containing 2mg/kg (0.7%) $^{13}$C$_6$-glucose administered by IV push (1 min)
- Specimens collected at t= -1, 2, 3, 4, 5, 6, 10, 12, 15, 20, 30, 40, 60, 80, 100, 120, 140, 150, 180, 210, 240 min.
- Total Glucose & Insulin assayed
- Glucose Isotope ratio by mass spec
The Minimal Model of glucose kinetics yields the following measures:

- Hepatic glucose Production: HGP
- Insulin Sensitivity: Si
- Glucose injected
- Lipolysis: NEFA
- β-cell secretory ability: DI
- Glucose (G)
- Insulin (I)
• As before, Hostility was related to metabolic parameters only in African American Women

• Reasons for this are not immediately apparent, but may relate to the wider range of central adiposity and hostility levels in this group
Relationship of Hostility to BMI in African American Women

Relationship of Hostility to Epinephrine Change following glucose bolus in African American Women

Relationship of Hostility to Fasting NEFA in African American Women

Surwit et al. *Psychosomatic Medicine, 2009*
Relationship of Hostility to DI in African American Women

Hepatic Glucose Production

• Endogenous glucose production from the liver and kidneys was estimated by assessing the latency of suppression of endogenous glucose (non labeled) following the IV glucose bolus.
Latency Time of Endogenous Glucose Suppression During the IVGTT: Faster Suppression is better
Hostility was associated with increased time to suppression of endogenous glucose in African American women.

Surwit et al. 2010, *Obesity*
How Hostility Might Impact Fasting Glucose

- Hostility
- EPI
- Central Adiposity
- NEFA
- Endogenous Glucose Production
- Pancreatic Beta Cell Function
- Fasting Glucose
Does Serotonin Metabolism Play a Role in the Relationship of Hostility to Metabolic Function?
Methods

Sample
37 healthy African American women. Mean age 32 years.

Measures
Hostility was assessed by a 27-item version of the Cook-Medley Hostility Scale. Tryptophan (TRYP), 5-OH-tryptophan (5HTP) and 5HIAA was assayed from cerebrospinal fluid drawn after lumbar puncture. Glucose and insulin were assayed from blood samples drawn after an overnight fast.
# Associations Among Study Variables

<table>
<thead>
<tr>
<th></th>
<th>TRYP</th>
<th>5HTP</th>
<th>5HIAA</th>
<th>Hostility</th>
<th>Glucose</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRYP</td>
<td>1.00</td>
<td>.37*</td>
<td>.01</td>
<td>-.03</td>
<td>-.06</td>
<td>.16</td>
</tr>
<tr>
<td>5HTP</td>
<td>1.00</td>
<td>.52**</td>
<td>.43**</td>
<td>.42**</td>
<td>.56**</td>
<td></td>
</tr>
<tr>
<td>5HIAA</td>
<td>1.00</td>
<td>.46**</td>
<td>.38*</td>
<td>.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>1.00</td>
<td>.52**</td>
<td>.41**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>1.00</td>
<td></td>
<td>.68**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* P<.05, **P<.01

Boyle et al, in preparation
Common Factor Analysis

A common factor analysis performed on age-adjusted hostility scores, fasting glucose and insulin, 5HTP and 5HIAA yielded a single factor (Eigenvalue = 2.31) in which all variables loaded above .55.
• This is consistent with studies that show that an SSRI (citalopram) successfully reduces hostility and improves metabolic parameters in high hostile individuals. Kamarck et al, Psychosomatic Medicine, 2009, Psychoneuroendocrinology, 2011).
CNS Serotonin, not Hostility, May Be the Causal Variable
Summary

• Stress and epinephrine interact with central adiposity in determining fasting glucose and pe-diabetes.

• Abnormal glucose metabolism could be due, in part, to a failure of the adrenal medulla to adapt to increasing adiposity.

• CNS serotonin metabolism is related to hostility, fasting glucose and insulin.

• Altered central serotonin metabolism could be driving all of these relationships.
Why Recommendations for Pre-Diabetes?

- 57 million people in the US have pre-diabetes
- Worldwide, number of people with pre-diabetes is estimated at 314 million
- Projected to be 418 million worldwide by 2025

Pre-diabetes raises the short-term absolute risk of type 2 diabetes by 3- to 10-fold, with some populations exhibiting greater risk than others.
Collaborators

- Anastasia Georgiades
- James Lane
- Mark Feinglos
- Cynthia Kuhn
- Redford Williams
- Sharon Minda
- David Millington
- Haoyue Zyang
- Raymond Boston
- Rhonda Merwin
- Ilene Siegler
- John Barefoot
- Stephen Boyle
- Rima Kaddurah-Daouk
- Clifton Bogardus
And Last, but not least, I would like to recognize my little friends who helped open the doors to this area of research.
Thanks to you for your attention!