There’s more to diabetes than insulin and insulin resistance.
WOMEN, DIABETES AND HORMONES

- OBESITY, RACE, POVERTY
- CORTISOL
- GROWTH HORMONE
- THYROID HORMONE
- HORMONES & OBESITY
- TESTOSTERONE, ESTROGEN
WOMEN, DIABETES AND OBESITY

• More than half of patients with DM in US are women.
• 95% of women with DM have type 2 DM
• Nearly half (47%) the women with diabetes have a body mass index greater than 30 compared with 25% of all women.
RELATIONSHIP BETWEEN BMI AND DM2 IN MEN AND WOMEN IN US

WOMEN, DIABETES AND RACE

• Minority women are especially burdened by diabetes.
  – Among non-white women, diabetes is the fourth leading cause of death.
  – The lifetime risk for diabetes for people born in the U.S. is 1 of 3; however, the risk is 1 in 2 for Hispanic women.

• “Biologic basis for ethnic differences in diabetes has not been elucidated.” Shai, Diabetes Care, 29(7), July 2006
  – Insulin resistance and obesity are major contributors to DM2 risk in persons of color.
OBESITY AND RACE

2005–2008 data from the National Health and Nutrition Examination Survey

• Obesity among women at age 20 years or older
  – 51% of non-Hispanic blacks
  – 43% of Mexican Americans
  – 33% of whites.

• Obesity among females aged 2–19 years
  – 24% of non-Hispanic blacks
  – 19% of Mexican Americans
  – 14% of whites
BMI is higher in black girls versus white girls, and starts to diverge after age 9.

Divergence of BMI for blacks and whites at the 85th percentile of BMI starts at age 9 and increases to 6.9 kg/m² at age 19. Pediatrics. 2001 Mar;107(3):E34. Racial divergence in adiposity during adolescence: The NHLBI Growth and Health Study
OBESITY AND RACE

• Earlier puberty in black girls than other girls
• Skin fold thickness and BMI were significantly higher for black girls than white girls starting at an early age, and continuing through age 19, very pronounced at the 85th percentile.
  – BMI at 85th percentile for black girls was 6.9 kg/m² greater than that for whites
• Differential rates of physical activity between races was postulated in 2001 NHLBI study to be related to the divergence in weight at an early age, but there may have been racial differences in reporting of physical activity that confounded this theory.
Median habitual activity (in metabolic equivalent times [METs] per week).
• black girls; □ white girls.

Bloomgarden Z T Dia Care 2004;27:998-1010 on the Diabetes Epidemic in Children

Age-adjusted means of BMI during 20 years of follow-up among 78,419 women by ethnic group.

Nurses Health Study 1980-2000
Shai I et al. Dia Care 2006;29:1585-1590

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After accounting for BMI, Nurse’s Health study indicated that Asians, Hispanics, and Blacks were all at higher risk for type 2 diabetes than whites.

Association between increasing BMI and greater weight gain and risk of diabetes was most pronounced among Asians.

- RRs were 2.26 for Asians, 1.86 for Hispanics, and 1.34 for Blacks.
INCREASE OF DM2 IN CHILDHOOD AND ADOLESCENCE

“Parallels the alarming rise in the number of young people who have become overweight or obese.”

Rate of new cases of type 1 and type 2 diabetes among youth aged <20 years, by race/ethnicity, 2002–2005

Source: SEARCH for Diabetes in Youth Study
NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics; API=Asians/Pacific Islanders; AI=American Indians
Neighborhoods, Poverty, Obesity and Diabetes

- Moving to Opportunity Demonstration Project Baltimore, Boston, Chicago, Los Angeles, and New York
- Families in impoverished census tracts (poverty of 40% or more) were recruited 1994-1998 & followed until 2008-2010
- Vouchers to subsidize housing were given for families to a) move neighborhoods to less impoverished census tract, b) to move to an area of their choosing without restriction, or c) control group got no vouchers

4498 families randomized

One woman in each family was interviewed; usually the household head

Outcome measures:
BMI
A1C

**Table 1. Baseline Characteristics of the Study Population.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Low-Poverty Voucher (N = 1425)</th>
<th>Traditional Voucher (N = 657)</th>
<th>Control (N = 1104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td>number (percent)</td>
<td>number (percent)</td>
</tr>
<tr>
<td>Age‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤35 yr</td>
<td>196 (14.6)</td>
<td>94 (13.5)</td>
<td>163 (14.7)</td>
</tr>
<tr>
<td>36–40 yr</td>
<td>310 (21.5)</td>
<td>156 (23.9)</td>
<td>253 (23.3)</td>
</tr>
<tr>
<td>41–45 yr</td>
<td>347 (23.5)</td>
<td>143 (21.7)</td>
<td>257 (23.2)</td>
</tr>
<tr>
<td>46–50 yr</td>
<td>273 (18.6)</td>
<td>124 (20.5)</td>
<td>194 (17.1)</td>
</tr>
<tr>
<td>&gt;50 yr</td>
<td>299 (21.7)</td>
<td>140 (20.4)</td>
<td>237 (21.7)</td>
</tr>
<tr>
<td>Race or ethnic group‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>973 (65.0)</td>
<td>393 (63.9)</td>
<td>706 (66.1)</td>
</tr>
<tr>
<td>Other nonwhite</td>
<td>339 (28.1)</td>
<td>194 (27.6)</td>
<td>288 (26.8)</td>
</tr>
<tr>
<td>White</td>
<td>92 (8.5)</td>
<td>52 (7.1)</td>
<td>88 (6.9)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>404 (31.5)</td>
<td>235 (33.0)</td>
<td>346 (30.3)</td>
</tr>
<tr>
<td>Never married</td>
<td>874 (62.6)</td>
<td>395 (63.5)</td>
<td>692 (64.3)</td>
</tr>
<tr>
<td>Age &lt;18 yr at birth of first child</td>
<td>347 (25.1)</td>
<td>163 (28.0)</td>
<td>265 (25.0)</td>
</tr>
<tr>
<td>Employed</td>
<td>368 (27.1)</td>
<td>176 (26.0)</td>
<td>258 (23.9)</td>
</tr>
<tr>
<td>Enrolled in school</td>
<td>216 (16.0)</td>
<td>113 (17.7)</td>
<td>172 (16.9)</td>
</tr>
<tr>
<td>Received high-school diploma</td>
<td>565 (38.3)</td>
<td>233 (34.3)</td>
<td>407 (35.9)</td>
</tr>
<tr>
<td>Received certificate of General Educational Development (GED)</td>
<td>235 (16.2)</td>
<td>124 (18.7)</td>
<td>204 (19.9)</td>
</tr>
<tr>
<td>Receives Supplemental Security Income‡</td>
<td>221 (15.9)</td>
<td>107 (17.1)</td>
<td>171 (16.3)</td>
</tr>
</tbody>
</table>
Women in low-poverty vouchers group versus control group had

- lower prevalences of BMI of 35 or more ($-4.61\%, P = 0.02$) and BMI of 40 or more ($-3.38\%, P = 0.03$), relative reductions of 13.0% and 19.1%.
- lower prevalence of glycated hemoglobin levels of 6.5% or more ($-4.31\%, P = 0.02$), a relative reduction of 21.6%.
Neighborhoods, Poverty, Obesity and Diabetes

The opportunity to move from a neighborhood with a high level of poverty to one with a lower level of poverty was associated with modest but potentially important reductions in the prevalence of extreme obesity and diabetes.

The mechanisms underlying these associations remain unclear.

There’s more to diabetes than insulin and insulin resistance.
DIABETES AND HORMONES

- Cortisol
- Growth hormone
- Thyroid hormone
- Hunger and satiety
  - Ghrelin
  - Leptin
- Testosterone and Estrogen
“Those durn adrenals....”
DIABETES AND HORMONES

CORTISOL

• Decreases hepatic and extrahepatic (muscle) sensitivity to insulin.
• Increases lipoprotein lipase in abdominal adipocytes, increasing abdominal fat.
• Obesity is associated with high urine free cortisol, normal serum cortisol, normal ACTH, increased cortisol clearance, and increased response to CRH.
• Metabolic syndrome is characterized by hyperactivity of the HPA axis, which leads to “functional hypercortisolism.”

Douyon Endoc Met Clin N Amer 2002 Mar; 31(1) 173-89
• Endogenous mediator of illness-related insulin resistance and hyperglycemia.

• Hospitalized patients.
  – High serum cortisol and urine free cortisol in acute ischemic stroke.
  – Acute stroke mortality related to increasing serum cortisol levels.

• Data on hypercortisolemia in OSA patients is inconclusive.

Journal of the Neurological Sciences, 2004 217(2);15:175-180
Journal of Internal Medicine 1990; 228(2):177-181
Sleep Med Rev 2011 Jul 29 e pub Tomfohr et al.
• Cushing’s syndrome
  – New onset diabetes and hyperglycemia.
  – Facial plethora, bruising, buffalo hump, abdominal obesity, muscle wasting and weakness, hypokalemia, fluid retention, hypertension, infections.

• Exogenous corticosteroids raise glucose, induce hyperglycemia, and increase insulin requirements in preexisting diabetes.
  – Post transplant, COPD, cancer treatment.
DIABETES AND HORMONES

GROWTH HORMONE

- Contributes to insulin resistance and dawn phenomenon in puberty.
- Obesity is associated with low GH, normal IGF1, increased GH BP and decreased GH response to GHRH.
- Cases of acromegaly
  - Diabetes and IGT

Douyon Endoc Met Clin N Amer 2002 Mar; 31(1) 173-89
• Thyroid diseases are found commonly in patients with diabetes.
• Increases in plasma thyroid hormone levels (hyperthyroidism or even subtle changes within the normal range) impair the ability of insulin to suppress hepatic glucose production and to increase glucose uptake in muscle.
• Endogenous overt hyper- and clinical hypothyroidism are both associated with insulin resistance.

Glucoregulatory Function of Thyroid Hormones: Interaction with Insulin Depends on the Prevailing Glucose Concentration  
*JCEM* July 1, 1986 vol. 63 no. 1 62-71

Thyroid hormones are positively associated with insulin resistance early in the development of type 2 diabetes.  
THYROID DISORDERS AND INSULIN RESISTANCE

The Interface Between Thyroid and Diabetes Mellitus
• Results of measures of insulin resistance and TFTs are inconsistent over multiple studies of
  – euthyroid patients,
  – metabolic syndrome,
  – subclinical hypothyroidism.

• Inconclusive evidence to support use of T3 in patients with hyperglycemia and early DM2.

• Decreased insulin clearance and hypoglycemia in hypothyroid patients on insulin.

• Hyperglycemia in hyperthyroid patients.
BRAIN-GUT AXIS

Int J Pept 2010; 817457, Wisser “Interactions of GI Peptide Ghrelin and its Anorexigenic Antagonists”
Control of food intake behavior and energy homeostasis relies on complex interaction between humoral components.
MY GHRELIN MADE ME DO IT
Diabetes and Hormones

GHRELIN

- Discovered in 1999
- Gut hormone made mostly in the stomach, some in pancreas/pancreatic islets, small intestine.
- 28 amino acid peptide
- The only peripherally produced peptide that stimulates food intake.
- Receptors in pancreatic islet cells

Tong, Diabetes 2010 Sept 59(9): 2145-57
Wisser, Int J Peptides 2010:817457
Diabetes and Hormones

**GHRELIN**

- Causes hunger and action is mediated in the hypothalamus.
- Ghrelin increases before meals and with fasting, and goes down or is “suppressed” after a meal.
- Chronic underfeeding increases ghrelin, and chronic overfeeding decreases ghrelin.
- Ghrelin level tends to be inversely related to body weight.
- A physiologic regulator of insulin and glycemia.

Diabetes and Hormones

GHRELIN

• Has several actions that could promote metabolic syndrome:
  – It inhibits insulin release and elevates glucose, stimulates feeding, and increases adiposity.

• In contrast it stimulates release of growth hormone, which hormone decreases fat mass and increases muscle mass.

• Future research:
  – how ghrelin and its receptor in islets are regulated.
  – precise and relative roles of islet-derived and stomach-derived ghrelin.

• “We can be curious for the next decades of ghrelin and its role in appetite regulation.”

Brownley K A et al. JCEM 2004;89:4457-4463,
Long-Term Persistence of Hormonal Adaptations to Weight Loss

50 overweight or obese patients without diabetes in a 10-week weight-loss program.

Meals replaced with (Optifast VLCD, Nestlé) and 2 cups of low-starch vegetables (500 to 550 kcal) per day.

Hormones measured at baseline, 10 weeks (after program completion), and 62 weeks.

Goal was 10% weight loss in 10 weeks.

One year after initial weight reduction, levels of the circulating mediators of appetite that encourage weight regain after diet-induced weight loss do not revert to the levels recorded before weight loss.

In obese persons who have lost weight, multiple compensatory mechanisms encouraging weight gain, which persist for at least 1 year, must be overcome in order to maintain weight loss.

Mean (±SE) Changes in Weight from Baseline to Week 62.

Mean (±SE) Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks.

• Individuals suffering from Prader-Willi syndrome
  – a genetic disorder characterized by a chronic feeling of hunger
  – high plasma ghrelin levels
  – individuals have severe obesity
Diabetes and Hormones

LEPTIN

- First described in 1994
- Secreted from adipose tissue in direct proportion to fat content
- Crosses the blood-brain barrier
- Interacts with leptin receptors in the hypothalamus and brainstem
- Inhibits food intake and increases energy expenditure
- Satiety hormone - “anorexigenic”
- Leptin and ghrelin induce opposite effects on food intake.
Diabetes and Hormones

LEPTIN

- Leptin levels are higher in females, even before puberty, compared with males
  - independent of differences in body composition
- Estrogens may be modulators of leptin's catabolic action in the brain.
  - Higher levels of estrogens have been associated with increased leptin sensitivity.
Diabetes and Hormones

LEPTIN AND ESTROGEN

• After puberty, estrogens and testosterone further modulate leptin synthesis and secretion.
  – Leptin receptor long form (leprb) is colocalized with Erα in hypothalamus.
  – Estrogens have been reported to regulate the expression of leprb mRNA in the arcuate nucleus of hypothalamus.

Published online 2009 July 8. doi: 10.2337/db 09-0257

Brain Research 2 September 2010, Pages 77-85
Neural Mechanisms of Ingestive Behaviour and Obesity
Two-hour postprandial mean (± se) leptin (top) and ghrelin (bottom) in obese and nonobese white and black women.

Leptin was high in obese women.

Postprandial Ghrelin was elevated in black compared with white women, independent of BMI.

Not inversely related to BMI in this study.
Independently, ghrelin was elevated in black women and leptin levels were elevated in obese women.

The subset of obese, black women exhibited the highest overall ghrelin and leptin levels.

Ghrelin levels appeared to be independent of central obesity in the subset of obese black women, an unexpected finding.

In white women, the expected inverse relationship between central obesity and ghrelin was obtained.

Higher ghrelin was associated with higher 24 h urine free cortisol only in black women and higher resting heart rate only in white women.

Higher ghrelin was linked to higher diastolic BP and lower norepinephrine in both black and white obese women.
• Endogenous sex hormones may differentially modulate glycemic status and risk of type 2 diabetes in men and women.

• High testosterone levels are associated with higher risk of type 2 diabetes in women but with lower risk in men.

• Low SHBG is associated with higher diabetes risk, which relationship is stronger in women than in men.
  – Women with type 2 diabetes had significantly lower plasma levels of SHBG than did controls.

Ding et al. JAMA 2006;295:1288-1299
TESTOSTERONE IS HIGHER IN CASES OF DIABETES IN PRE- AND POST MENOPAUSAL WOMEN
DIABETES AND HORMONES

ESTROGEN

Retrospective review, 1966-2005, of 43 prospective and cross-sectional studies, 726 men and 625 women

• “Question of direct relationship between plasma estradiol and risk of DM2 is less certain” than associations of testosterone and DM2.
• Elevated levels of estradiol in type 2 diabetes were suggested among both men and post menopausal women with no apparent sex dimorphism.
• Studies internally controlled for BMI showed that estradiol was still associated with type 2 diabetes.

Ding et al. JAMA 2006;295:1288-1299
Estrogen and estrogen signaling (Erα, Erβ) regulate glucose homeostasis, help maintain normal insulin sensitivity.

Low estrogen levels (menopause or ovariectomy)
- associated with increased food intake, increased visceral fat accumulation, may promote insulin resistance and DM2

OCP and HRT effects:
- decreased fasting plasma glucose, improved glucose tolerance, decreased food intake, increased insulin secretion.

Brown et al. Brain Res. 2010; 1350:77-85
Faulds, Dahlman-Wright, Update on Mechanisms of Hormone Action
Fig. 4. Estrogen influences glucose metabolism in the central nervous system (CNS), pancreatic $\beta$ cells, muscles, liver and adipocytes.
Future research:
“Identifying critical brain sites where estrogen receptors regulate body weight homeostasis...”

Brown et al. Brain Res. 2010; 1350:77-85
WOMEN, DIABETES AND HORMONES

• Complex system of interrelated hormones which affect diabetes and diabetes risk.
• Women are particularly influenced by diabetes risk factors of race and obesity.