PCOS Awareness Symposium 2015
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The PCOS - Diabetes Connection
Preventing Stroke, Kidney Disease, Liver Disease & Other Complications

Katherine Sherif, MD
Professor & Vice Chair, Department of Medicine
Director, Jefferson Women’s Primary Care
Thomas Jefferson University
Type 2 Diabetes

- 3rd leading cause of death in US
- By the time of diagnosis with T2D, you have been insulin resistant for at least 12 years
Increased conversion to diabetes

- Nurses Health Study: 101,073
  - 8 year period
  - Conversion to type 2 diabetes was double in women who were oligomenorrheic compared to women who were eumenorrheic

- 27% of women with type 2 diabetes had PCOS

JAMA 2001; 286:2421–2426
Diab Care 2001; 24:1050–1052
Prevalence of IGT & diabetes
Thin vs. obese PCOS

Legro, JCEM 1999
PCOS: Prevalence of IGT & diabetes

- 35% have IGT
- 10% have diabetes
PCOS & weight-matched controls

- PCOS women have a higher *prevalence* of hyperinsulinemia
  - Clin Endocrinol Metab 1987;65:499–507

- PCOS women have a *greater degree* of hyperinsulinemia
  - Diabetes 1989;38:1165–1174

- 16% of PCOS developed diabetes at menopause compared to 6% of obese women
Insulin resistance underlies T2D

- Insulin resistance
- Impaired glucose tolerance
- Impaired fasting glucose
- Type 2 diabetes
What is insulin resistance?

- The body RESISTS taking sugar into the cells
- Insulin can’t link with the receptors on the surfaces of cells because there aren’t enough receptors
- Something goes wrong in the chemical reaction at the time of linking
- The body can’t use the sugar in the blood & hi BG develops bringing on DM symptoms
Causes of insulin resistance

- Combination of genetic and lifestyle factors
- Heredity
- Ethnic group--NA, AA, Latinas, South Asians
- Abdominal obesity interferes w/ insulin action
- Lack of exercise and high caloric diet
- Stressful lifestyle—stress hormones released
- Pregnancy-increase in weight and production of placental hormones raise glucose
• Certain proteins and/or enzymes released by stored fat act on muscle and liver cells to impair the way they “read” insulin signals to process glucose

• Visceral abdominal fat sheds more free fatty acids; elevated TG levels increases insulin production promoting further fat storage
How does abdominal fat cause IR?

- Abdominal fat continuously releases TG into the branch of the bloodstream that feeds the liver.
- This increases the body’s need for insulin.
- Demand for more insulin causes pancreas to work harder to produce elevated insulin levels.
- High levels of insulin in blood down-regulate the affinity for insulin that insulin receptors all over the body have naturally-“tolerance” causes > IR.
What defines insulin resistance?

- Hyperglycemia
- Dyslipidemia - high triglyceride, low HDL
- Central obesity
- Elevated blood pressure - greater than 130/80
How important is control?

- For every 1% rise in Hb A1c:
  - there is an 18% rise in risk of heart attack

- Tight blood sugar control reduces risk of CVD

**Goals:**
- **FBS – pre-meal** <110,
- **Post-meal** <180
- **HbA1c** <7%
Examine your blood tests

- Liver function tests: AST, ALT – the lower, the better
- Creatinine (blood) – the lower, the better
- A1c (or hemoglobin A1c) – the lower, the better
- Triglycerides – the lower, the better
Link with Coronary Artery Disease

- Coronary angiography: women with polycystic ovaries have more extensive CAD
  - “extensive” = number of segments with >50% stenosis

- NHS: oligomenorrheic women followed for 8 years had double the risk of fatal MI

- Retrospective study – oligomenorrheic women in the 1950’s were 7.4 x’s more likely to have MI in their 50’s and 60’s

Birdsall, Annals Int Med, 1997
Dahlgren, Acta Obstet Gynecol Scand, 1992
Pathophysiology

Theca cell

androstenedione & T → Grunulosa

Progesterone → 17α - OH P

LH

↑ GnRH pulsatility

testosterone estrone

Peripheral conversion

estradiol

A* = aromatase
Pathophysiology

- Insulin
  - ↓ SHBG

- Theca cell
  - androstenedione → testosterone
  - testosterone → estradiol

- LH
  - ↑ LHRH pulsatility
  - ↑ LH
  - testosterone
  - estrone

- Progesterone
  - → 17α - OH P

- Follicle
  - ↑ Free T
  - Peripheral conversion
## Traditional Treatment

- Oral contraceptives
  - Oligomenorrhea
  - Hirsutism
  - Acne
  - Alopecia

- Anti-androgens
  - Hirsutism
  - Alopecia

- Clomiphene
  - Infertility
Hyperinsulinemia

- Testosterone
  - Acne
  - Hirsutism
  - Anovulation
  - Infertility

- Ovary

- Endothelium
  - Endothelial dysfunction
  - Dyslipidemia
  - Diabetes
  - Hypertension

- Overweight
  - Acanthosis nigricans

Sherif 2006 ©
Traditional treatment does not address hyperinsulinemia.
Key: decrease insulin resistance

- Nutrition
  - Decrease simple carbohydrates
  - Decrease calories

- Increase physical activity

- Insulin-sensitizing medications

- Insulin-sensitizing supplements
Multiple Signs & Symptoms

Irregular periods, Bleeding too much, Bleeding too little, Anxiety, Depression, Eating disorders, Weight gain, Acanthosis nigricans, Skin tags, Follicular keratitis, Hirsutism, Acne, Alopecia, Excess sweating, Seborrheic dermatitis, Hidradenitis supparativa, Fatty liver, High triglycerides, low HDL-cholesterol, Elevated glucose, Infertility, Breastfeeding problems, Poor sleep, Miscarriages, Fatigue, Endometrial cancer
Prescription for Treatment

Goals

- Dermatologic symptoms caused by androgens
  - Hirsutism
  - Acne
  - Alopecia
  - Excess sweating
  - Seborrheic dermatitis
  - Hidradenitis supparativa
Prescription for Treatment

Goals

- Symptoms directly related to insulin resistance
  - Weight gain
  - Acanthosis nigricans
  - Skin tags
  - Follicular keratitis
Prescription for Treatment

Goals

- Psychologic/psychiatric symptoms
  - Anxiety
  - Depression
  - Eating Disorders
Prescription for Treatment

Goals

- Metabolic problems
  - Fatty liver
  - High triglycerides and low HDL-cholesterol
  - Elevated A1c (3-month sugar)
Prescription for Treatment

Goals

- Infertility
- Sleep apnea
- Difficulty breastfeeding
Key: decrease insulin resistance

- Nutrition
  - Decrease simple carbohydrates
  - Decrease calories
- Increase physical activity
- Sleep
- Insulin-sensitizing medications
- Insulin-sensitizing supplements
Improve Insulin Sensitivity
Medications that may decrease weight

- Insulin Sensitizers
  - Metformin
  - TZD’s – thiazolidinediones (Actos, Avandia)

- Incretins – derived from the Gila Monster
  - Byetta → Bydureon (weekly)
  - Victoza → Saxenda (weekly)
  - Trulicity
  - Symlin
Improve Insulin Sensitivity:
Weight Loss Medications that *do not* improve insulin sensitivity.....but when you lose weight, you are more insulin sensitive

- Phentermine
- Topamax
- Qsymia = phentermine and Topamax
- Belviq – affects brain serotonin
- Contrave = naltrexone and bupropion

- Alli (Xenical)
Metformin

- Benefits:
  - Weight loss (minimal)
  - Improved lipid profile
  - Improved acne, hirsutism and alopecia
  - Normalization of transaminases
  - Ovulation & pregnancy
    - Cochrane meta-analysis: first-line agent for anovulation

- Side effects
  - Gastrointestinal: diarrhea, nausea
  - Decreased B-12 absorption and ↑ homocysteine

Lord, BMJ, 2003
Treatment

- Metformin ER: 500mg titrated up to 2000mg/day
- Pioglitazone and rosiglitazone
  - Associated with fluid retention
- Byetta, Symlin, Victoza
- Spironolactone: dose-dependent
Thiazolidinediones

- May be more effective in thin PCOS

- Thiazolidinediones (TZD’s or glitazones)
  - Troglitazone – most studied
  - Pioglitazone
  - Rosiglitazone
  - Both associated with fluid retention

- Check liver function tests in 4 weeks
Anti-androgens

- Spironolactone 100mg twice a day**

- May take as long as 3-6 months to see improvement, especially in alopecia

- Alpha-reductase inhibitors: saw palmetto, flutamide, finasteride
  - Transaminase elevations

- Ornithine decarboxylase inhibitors: eflornithine
  - 30% “response” rate at six months
Treatment with insulin sensitizers improves fertility & CVD risk factors

Decrease hyperinsulinemia

↓ testosterone

↑ ovulation

improve endothelial function

↓ hyperandrogenemia

fertility  endometrial ca

Hirsutism, Acne, Alopecia

BP, lipids, glucose

↓ Cardiovascular risk
Treatment

- Ovulation occurs in most within 3 months
  - May be as early as 1 month or prior to first menses
  - Must discuss risk of pregnancy within the first month

- If pregnancy desired
  - Discuss use of metformin during pregnancy
  - Most obstetricians ok with metformin during pregnancy
  - Stop pioglitazone and rosiglitazone asap
Supplements with insulin-sensitizing properties

- Omega-3 fatty acids
- Cinnamon
- Vitamin D
- Chromium
- N-acetyl cysteine**
- Resveratrol
- Alpha lipoic acid
- Magnesium**
- D - chiro inositol & Myo-inositol
Prescription Plan

- Address the basics that improve insulin sensitivity
  - Nutrition
  - Physical activity
  - Sleep

- Are your symptoms due to high testosterone or high insulin or both?

- Think about what direction you want to go in when you’re 50 years old: commit now to live