PCOS, Type 2 Diabetes Mellitus, Metabolic Syndrome: How to assess and manage the many faces of insulin resistance

Developed and presented by:
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Disclosure

• No real or potential conflict of interest to disclose.
• Off label—The use of metformin in PCOS will be discussed.

Objectives

• Having completed the learning activities, the participant will be able to:
  – Describe the characteristics insulin resistance as part of the disease process in type 2 diabetes mellitus (DM), metabolic syndrome and polycystic ovary syndrome (PCOS).
Objectives (continued)
- Having completed the learning activities, the participant will be able to: (cont.)
  - Identify the mechanism of action and therapeutic benefits for standard and newer medications used to prevent and treat the above-mentioned conditions and their utility in the patient with insulin resistance who is having difficulty getting to treatment goals.

References
Listed within the Presentation

What is insulin resistance?
- Defined
  - State in which a given concentration of insulin produces a less-than-expected biological effect
- Alternative criteria
  - Requirement of ≥200 units of insulin per day to attain glycemic control and to prevent ketosis
  - Source: https://www.ncbi.nlm.nih.gov/pubmed/11460565
With Insulin Resistance

- To maintain NL glucose
  - Patient can produce 5–8 × as much insulin per day when compared to non IR person.
  - Estimated endogenous “dose” as high as 500 units/d
    - Source: AACE Diabetes Guidelines, Endocr Pract, 2002;8 (Supp 1)

Acanthosis Nigricans=Cutaneous Manifestation of Hyperinsulinemia
Consequences of Hyperinsulinemia = HTN, Difficult to Control HTN

- Enhances
  - Renal tubule reabsorption of sodium, leading to an increase in blood pressure
  - Meds counteracting this? Thiazide diuretics

(continued)

- Endothelial dysfunction via reduced nitric oxide production, leading to
  - Vasoconstriction, platelet aggregation, altered vessel membrane permeability and subsequent microalbuminuria
  - Meds counteracting this? ACEI/ARB, CCB

Effects of Increased Sympathetic Nervous System Activity in DM

- Increased
  - Blood pressure
  - Free fatty acid levels
  - Myocardial utilization of free fatty acids
  - Myocardial O₂ consumption
  - Myocardial ischemia
  - Proarrhythmic effects
  - Meds counteracting this? Alpha-beta blocker, beta blocker

Sources:
- Fonarow GC. AJM. 2004;116:76S-88S.
- Bell DSH. AJC. 2004;93:49–52.
HTN, CVD and IR

- Hyperinsulinemia effects
  - Increased vascular smooth muscle proliferation
  - Greater responsivity to angiotensin II
  - Enhanced sympathetic activation

What is the clinical consequence?

Hypertension
Dyslipidemia
Glucose intolerance
Major components of metabolic syndrome

Lifestyle Modification Recommendations in HTN, Dyslipidemia, IR

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Average SBP reduction rate</th>
</tr>
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<tbody>
<tr>
<td>Physical activity</td>
<td>Aerobic (90–150 min/wk)</td>
<td>Hypertension: -5/8 mm Hg</td>
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<tr>
<td></td>
<td>Dynamic resistance (90–150 min/wk)</td>
<td>Normotension: -2/4 mm Hg</td>
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<td>Hypertension: -4 mm Hg</td>
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<td>Normotension: -2 mm Hg</td>
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### Lifestyle Modification Recommendations in HTN, Dyslipidemia, IR (continued)

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<tr>
<th>Modification</th>
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<th>Average SBP reduction rate</th>
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<tbody>
<tr>
<td>Physical activity (cont.)</td>
<td>Isometric resistance (4 × 2 min [hand grip], 1 min rest between exercises, 3 sessions/wk)</td>
<td>Hypertension: -5 mm Hg</td>
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<td>Normotension: -4 mm Hg</td>
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### Are adipose cells simply fat storers or metabolically active?

- **Old thought**
  - Fixed state where these cells increase and decrease in size but not in number

### Are adipose cells simply fat storers or metabolically active? (continued)

- **Newer thought**
  - Secrete specialized cytokines (adipokine) including TNF
  - TNF exacerbates insulin resistance by desensitizing insulin receptors.
Are adipose cells simply fat storers or metabolically active?
(continued)

• “Adipose tissue also contains numerous macrophages, which provide a rich source of TNF- and interleukin-6, consistent with the view that adiposity is a form of chronic, low-grade inflammation.”

Visceral vs. Subcutaneous Fat

Fat is a problem, but does the way you get rid of it make a difference?

• Conclusion
  – Abdominal liposuction does not significantly improve obesity-associated metabolic abnormalities.
  – Decreasing adipose tissue mass alone will not achieve the metabolic benefits of weight loss.
International Diabetes Federation (IDF) Definition Metabolic Syndrome

- Central obesity (defined as waist circumference 37 inches [≥94 cm] for Europid men and 31.5 inches [≥80 cm] for Europid women, with ethnicity specific values for other groups)

International Diabetes Federation (IDF) Definition Metabolic Syndrome (continued)

- Plus any two of the following four factors
  - Raised TG level
    - ≥150 mg/dL (1.7 mmol/L) or TG elevation treatment
  - Reduced HDL cholesterol
    - <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females

International Diabetes Federation (IDF) Definition Metabolic Syndrome (continued)

- Plus any two of the following four factors (cont.)
  - Raised blood pressure
    - Systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg or treatment of previously diagnosed hypertension
  - Raised fasting plasma glucose (FPG)
    - ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes
Medications Aimed at Insulin Sensitization, Reducing Insulin Resistance

• Biguanide
  • Metformin
    – Inexpensive, 4+ decades of use data
    – Reduces free testosterone by approx. 25% in women with hyperandrogenism
    – Helpful at managing hyperglycemia, glucose intolerance, prevention of T2DM

Metformin for DM Prevention

• Metformin therapy for prevention of type 2 diabetes can be considered in those at highest risk for developing diabetes, such as those with multiple risk factors, especially if demonstrated progression of hyperglycemia (i.e., A1c ≥6% [0.06 proportion]) despite lifestyle interventions.
  – 1500–2000 mg per day as typical dose

True or false?

Metformin use is potentially associated with the following changes in lipid profile:
  ↓ LDL, ↑ HDL, ↓ TG. Yes
Metformin use increases risk of vitamin B₁₂ deficiency due to B₁₂ malabsorption, risk appears dose- and length-of-therapy-dependent. Yes
Should we focus on fasting glucose? Postprandial glucose?

• “Early and intensive glycemic control, using regimens which recreate a physiological insulin profile, controlling postprandial as well as fasting glucose levels, offers the most promise for preserving beta-cell function, decreasing disease progression, and reducing the chronic complications of diabetes.”
  

Should we be checking insulin or C-peptide levels?

• No specific test for degree of insulin resistance
  – Checking end-product of IR such as glucose status

• Not recommended
  – Insulin levels
  – C-peptide levels


C-peptide vs. Insulin Levels Produced at the Same Rate

• Insulin
  – Proinsulin or insulin antibodies interfere with insulin assays
  – Released from pancreas, large hepatic first-pass effect: End result= $T_{1/2}$ = 4 mins
  – Poor reflection of insulin status

  Image source: Created by Isaac Yonemoto
  https://commons.wikimedia.org/wiki/File:InsulinHexamer.jpg
C-peptide vs. Insulin Levels (continued)

• C-peptide
  – Connects insulin’s A-chain to its B-chain
  – More reliable indicator of insulin secretion
    • Not extensively hepatically cleared by the liver
    • T½=30 minutes

Image source: JaGa
https://commons.wikimedia.org/wiki/File:C-Peptide.svg

C-peptide vs. Insulin Levels (continued)

• Only C-peptide source
  – Endogenous insulin
    • Can help distinguish ability of pancreas to release insulin vs. exogenous insulin
    • Potentially helpful in distinguishing T1 from T2DM in a person who presents on exogenous insulin

Special Nutritional Consideration in IR

• Vitamin D
  – Suggest link between inability to maintain appropriate glucose levels and vitamin D deficiency
    • No specific target vitamin D level set
  – Minimum supplementation at vitamin D₃ 600 international units daily
Special Nutritional Consideration in IR (continued)

- Chromium picolinate
  - Supplements containing 200–1,000 mcg chromium as chromium picolinate a day have been found to improve blood glucose control.

- Magnesium deficiency
  - Associate with IR, no supplement recommendations
    - Source: [https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0058278](https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0058278)

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Source

The Diagnosis and Management of Nonalcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology

Definitions

- Fatty liver disease—The accumulation of fat in the hepatocyte
  - Alcoholic fatty liver disease (AFLD)
  - Nonalcoholic fatty liver disease (NAFLD)
- Hepatic steatosis
  - Another way of saying fatty liver disease

Nonalcoholic Fatty Liver Disease (NFLAD)

- Etiology
  - Triglyceride accumulation in hepatocytes
- Prevalence
  - 20 to 30% of adults in the general population in Western countries
  - 70 to 90% among persons who are obese or have diabetes

Nonalcoholic Steatohepatitis (NASH)

- Defined
  - Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis
NAFLD
Established Risk Factors

• Obesity
• Type 2 DM
• Dyslipidemia
• Metabolic syndrome
  – Source: https://www.gastrojournal.org/article/S0016-5085(12)00494-5/fulltext

NAFLD Risk Factors
Emerging Associations

• PCOS
• Obstructive apnea
• Hypothyroidism
• Hypopituitarism
• Hypogonadism

Nonalcoholic Steatohepatitis
Alcohol Abuse Excluded

• Initial findings
  – Elevated aminotransferase
    • Exclusion of viral, metabolic, other causes
• Histologic diagnosis
  – Liver biopsy findings similar to alcoholic liver disease including Mallory bodies, ballooning hepatocyte degeneration
NAFLD Lab Findings

- AST, ALT
  - Seldom >3 × ULN
- ALT:AST ratio
  - Usually >1
- ALP, GGT
  - Up to 2–3 × ULN in less than ½
- OK to take a statin? Yes

NAFLD Lab Findings (continued)

- Bilirubin, albumin, protime INR
  - Usually NL, particularly in earlier disease
  - Abnormalities usually mark advanced or severe hepatic disease

Liver Biopsy in NAFLD

- “Gold Standard” for diagnosis
- Helps rule in or out other diagnoses
NAFLD Treatment Options

• Lifestyle modification
  – Weight loss, increased physical activity aimed to better control glucose, enhance insulin sensitivity, improving lipid control

• Metformin
  – Helpful for glucose control but use does not alter histologic changes in NASH


Vitamin E (800 international units/d) was superior to placebo for the treatment of nonalcoholic steatohepatitis in adults without diabetes.

NAFLD Pharmacologic Therapy

• Pioglitazone 30—45 mg daily
  – Improved steatosis, inflammation and liver enzymes

• Adverse effect
  – Weight gain
  – Long-term effects in non-diabetics are unknown.
NAFLD Pharmacologic Therapy (continued)

- Glucagon-like peptide-1 agonists
  - Liraglutide once daily × 48 weeks was associated with greater resolution of NASH and less progression of fibrosis.
  - More studies are needed to determine if GLP-1 agonists could be considered specifically for the treatment of NASH.
  

IR in all tissues?

- Resistant to insulin action
  - Liver, adipose tissue, muscle
    - Pancreas produces more insulin to achieve desired effect
- Sensitive to insulin action
  - Ovary
    - High levels of circulating insulin lead to increased ovarian androgen production, hyperandrogenism

Pathophysiological Characteristics of Polycystic Ovary Syndrome (PCOS)

Rotterdam PCOS Criteria

- ≥2 of the following manifestations
  - Irregular or absent ovulation
  - Elevated levels of androgenic hormones
  - Enlarged ovaries containing at least 12 follicles each
    - If evidence of hyperandrogenism and oligo-ovulation, then imaging for polycystic ovaries not required.

- Other conditions ruled out
  - Source: https://emedicine.medscape.com/article/256806-overview

Diagnostic Testing in PCOS

- Transvaginal ultrasonography
  - Enlarged ovaries with increased stroma, multiple subcapsular small follicles
    - Present in 10–90% of women with PCOS but also up to 25% of women without the condition

Polycystic Ovaries with “String of Pearls” Appearance
Additional PCOS Consequences

• Increased androgens
  – Decreased SHBG production in response to hyperinsulinemia = more free androgen

Polycystic Ovary Syndrome
True or false?

• PCOS affects about 5 to 10% of women of childbearing age. True
• PCOS is the most common cause of anovulatory infertility in developed countries. True

Laboratory Evaluation in Suspected PCOS

• Largely aimed to rule out other conditions
  – TSH
    • Rule out hypothyroidism
  – Serum prolactin level
    • Evaluation of anterior pituitary function
Laboratory Evaluation in Suspected PCOS (continued)

- Largely aimed to rule out other conditions (cont.)
  - Serum 17-hydroxyprogesterone (17-OHPG) level
    - Evaluation of adrenal function
  - Free testosterone levels
    - Evaluation of hyperandrogenic state
- Additional testing as directed by patient presentation

PCOS Current Recommendations

- Evaluation should include
  - Excluding alternate androgen excess disorders
  - Risk factors for endometrial cancer
  - Mood disorders
  - Obstructive sleep apnea
  - DM
  - CVD

Emerging PCOS Treatment Options

- Omega-3 fatty acid supplementation to reduce liver fat content and cardiovascular risk factors
- Treating vitamin D deficiency
  - Source: https://emedicine.medscape.com/article/256806-overview
Acne and Hormones
What is the connection?

• What causes increased sebum production?
  – Abnormal circulating androgen levels present in majority of women with severe acne.
  – Part of PCOS pathophysiology

Estrogen supplementation
  – Increases available sex hormone binding globulin (SHBG)

Results
  – Lower free androgen levels
  – Also potentially lowers free estrogen levels

Spironolactone (Aldactone®)
  – Antiandrogen

COC Use in Women with Acne Vulgaris, PCOS

Low-dose OCs/Patch/Ring, Spironolactone=Antiandrogenic

• Improvement
  – Acne, usually after 3 months use
  – Hirsutism, usually after 6 months use
    • Typically with hirsutism, condition improvement is modest but does not worsen.
PCOS
Current Recommendations
- Hormonal contraceptives are the first-line management for menstrual abnormalities and hirsutism/acne in PCOS.
  - Best-studied choice and likely most clinically effective, combined hormonal contraception (estrogen/progestin) in pill, patch or ring.
  - Source: http://www.medscape.com/viewarticle/557087_1

Is “regulating the period” enough?
- “However, given the metabolic derangements associated with the polycystic ovary syndrome, it seems prudent and appropriate to plan long-term therapy that addresses not only management of the consequences of androgen excess and anovulation but also the new goals of ameliorating insulin resistance and reducing the risks of type 2 diabetes and cardiovascular disease.”

PCOS True or false?
- Only certain birth control pills can help with hirsutism. False
- Once under control, the woman can discontinue COCs or spironolactone and the acne and hirsutism will remained improved long-term. False
PCOS
True or false?
(continued)
• Women with PCOS are at increased risk for:
  – Endometrial cancer. True
  – Ovarian cancer. False
  – Hypertriglyceridemia. True

• In the woman with PCOS and amenorrhea who does not want to take COCs, cyclic progesterone/progestin therapy should be considered. True
  – Source: https://emedicine.medscape.com/article/256806-overview

Source: van der Vane et al. Contraception. 41:345-352.
www.contraceptiononline.org
PCOS
True or false?
(continued)
• In the woman with PCOS who wants to conceive, which of the following are treatment options to enhance ovulation?
  – Weight loss in overweight/obesity True
  – Clomiphene (Clomid®) 2nd-line for inducting ovulation

PCOS
True or false?
(continued)
• In the woman with PCOS who wants to conceive, which of the following are treatment options to enhance ovulation?
  (cont.)
  – Metformin Metformin helpful with menstrual regulation but not helpful for enhanced fertility.
  – Letrozole (Femara®) First-line for ovulation induction

End of Presentation
Thank you for your time and attention.
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