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Education by the Experts



RT103 Clinical Chemistry of the Metabolic Syndrome

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Before my career as a Clinical Chemist, I obtained my primary boards in Pediatrics and Pediatric Endocrinology.

I still attend in clinic one afternoon per month.

Below is a typical patient in my clinic. . . .

Jane was a 15-year-old African American female who was referred to Pediatric Endocrine clinic with the request to “r/o diabetes.”

Jane was the 9 lb 10 oz product of a term gestation. She was delivered vaginally without complications. Her developmental milestones were normal. Since age 5 she has been overweight. She is now 5’10” and weighs 220 lbs. Her menses are irregular. Her last menses was 3 months ago. She first menstruated at age 11.

Her referring MD is concerned about diabetes because she gets up at night to drink water and empty her bladder. Her 35-year-old mother is obese, had GDM and has been diagnosed with T2DM for 5 years. Her 60-year-old grandmother developed T2DM at age 40 and is now on dialysis.

PE: BP = 140/78 mmHg; centripetal obesity; darkened skin around her neck & under arms & breasts; no wasting of the arms or legs; pink abdominal stria; Tanner V breasts; Tanner IV pubic hair

How do we “r/o diabetes?”

ADA recommended screening test for DM:

- Fasting plasma glucose
 - easy
 - cheap
 - less sensitive than OGTT
 - more reproducible than OGTT

- OGTT is an acceptable alternative
 - FPG + 2 hr value following 75 g gluc.
 - more expensive
 - more sensitive
 - 2 hr: less reproducible than FPG

**How does the ADA define
(diagnose) diabetes?**

ADA definition of DM

- hyperglycemia on 2 separate occasions
(excluding DKA & NKHC)
- at least: 2 different days
- on OGTT: incr. fasting & 2 hr does NOT
equal “2 separate occasions”

**How is hyperglycemia
defined?**

Normal Hyperglycemia

Fasting <100 mg/dL =>126 mg/dL

2-hr <140 mg/dL =>200 mg/dL

Random* <200 mg/dL =>200 mg/dL

* symptoms must be present

What are fasting plasma glucose values between 100 and 125 mg/dL and between 140 and 199 mg/dL termed?

Range Terminology

Fasting	100-125 mg/dL	Impaired fasting glucose (IFG)
2-hr	140-199 mg/dL	Impaired glucose tolerance (IGT)

- Collectively termed “prediabetes”

Results of her OGTT

	<u>Result</u>	<u>Interpretation</u>
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FPG	95 mg/dL	Normal
2-hr	198 mg/dL	IGT

- She is “prediabetic” & counseled on diet/exercise.
- repeat OGTT is scheduled for 6 months

Is any other laboratory testing indicated?

Yes!

- Fasting lipid profile
- ALT
- Pregnancy test
 - a common cause of amenorrhea in women of reproductive age

**Why perform a lipid profile and
why measure an ALT?**

You are concerned that this adolescent may have the metabolic syndrome!

suggestive clinical features

- obesity
- acanthosis nigricans
- prediabetes
- oligomenorrhea

risk factors for T2DM

- ethnicity: minority
- strong family history of T2DM

What is the metabolic syndrome?

Metabolic syndrome

- is the name for a group of risk factors linked to overweight and obesity that increase the patient's chance for heart disease and other health problems such as diabetes and stroke.

What are alternative names for the metabolic syndrome?

Metabolic syndrome

- insulin resistance syndrome” (IRS)
- syndrome X
- dysmetabolic syndrome X (ICD-9: 277.7)*
- diabetes syndrome
- morbidity syndrome

**How can the metabolic syndrome
be defined clinically?**

NCEP, ATP III: Metabolic Syndrome*

=>3 of the following:

Abdominal Obesity Waist Circumference†

Men >102 cm (>40 in)

Women >88 cm (>35 in)

Triglycerides =>150 mg/dL

HDL-C

Men <40 mg/dL

Women <50 mg/dL

Blood pressure =>130/85 mmHg

Fasting glucose =>110 mg/dL

* The ATP III panel did not find adequate evidence to recommend routine measurement of insulin resistance (e.g., plasma insulin), proinflammatory state (e.g., high-sensitivity C-reactive protein), or prothrombotic state (e.g., fibrinogen or PAI-1) in the diagnosis of the metabolic syndrome. † Some male persons can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in). Such persons may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.

AMERICAN ASSOCIATION of CLINICAL ENDOCRINOLOGISTS (AACE)

Dysmetabolic Syndrome denotes a constellation of metabolic abnormalities in serum or plasma insulin/glucose level ratios, lipids (triglycerides, LDL cholesterol subtypes and/or HDL cholesterol), uric acid levels, coagulation factor imbalances and vascular physiology.

<http://www.aace.com/members/socio/syndromex.php>

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Major Features

Insulin resistance: denoted by hyperinsulinemia relative to glucose level or Acanthosis Nigricans

Central Obesity: waist: men: >40 in; women: >35 in

Dyslipidemia: HDL-C: men <35 mg/dL; women <45 mg/dL, or triglycerides >150 mg/dl

Hypertension

Impaired fasting glucose or Type 2 diabetes

Hyperuricemia

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Minor Features

Hypercoagulability

Polycystic ovary syndrome

Vascular endothelial dysfunction

Microalbuminuria

Coronary heart disease

AACE: do not state how many criteria are required to diagnose dysmetabolic syndrome X.

WORLD HEALTH ORGANIZATION (WHO)

Htn (>140/90 mmHg)

Tg >150 mg/dL &/or, in men, HDL-C <35 mg/dL; in women, HDL-C <40 mg/dL

BMI >30 kgM⁻² , W/H ratio: >0.9 (men), >0.85 (women)

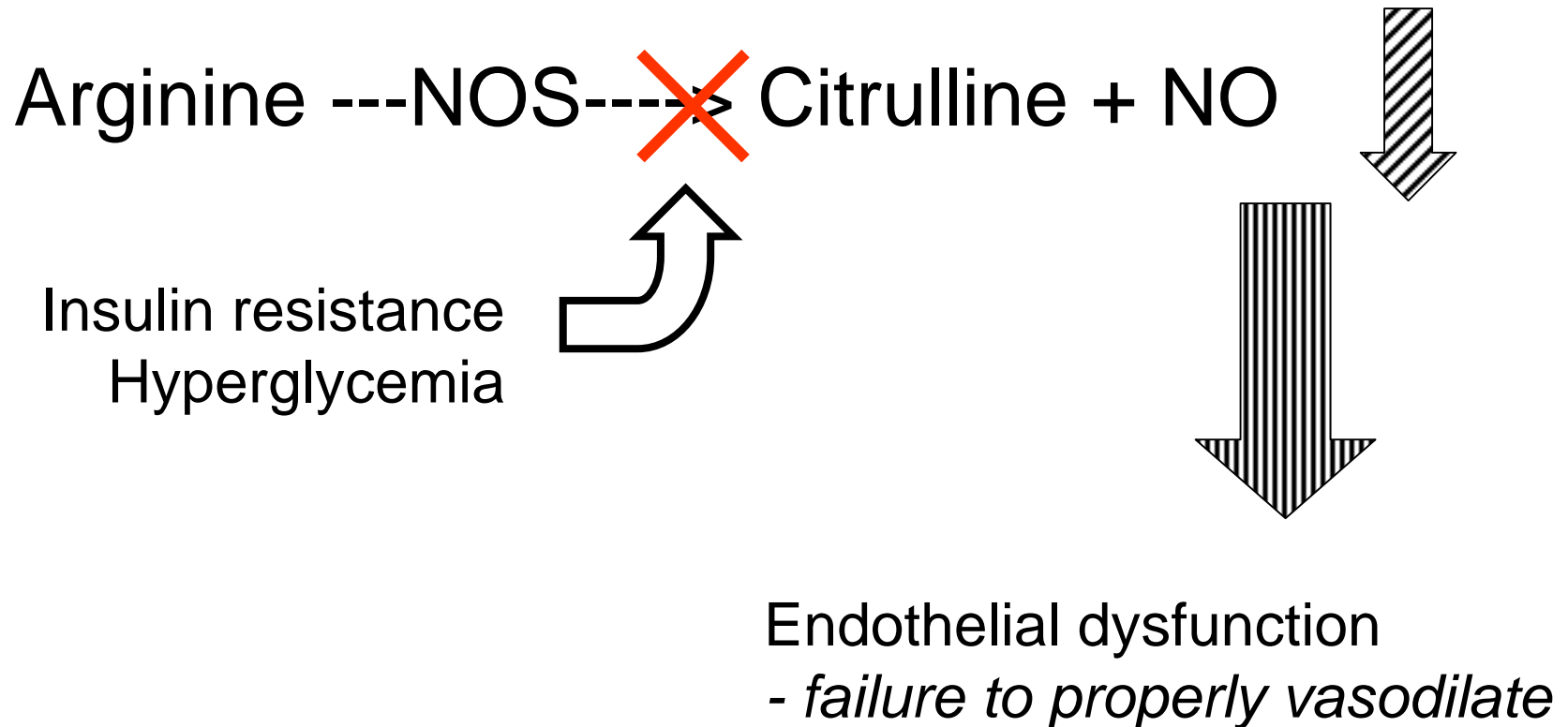
T2DM or IGT

Microalbuminuria (AM: >20 mg/min (30mg/g Cr)

Confirmed: T2DM or IGT (+) 2 criteria
 NI GT (+) 3 criteria

**What does microalbuminuria
indicate in the absence of
diabetes?**

Vascular endothelial dysfunction: An early finding in the metabolic syndrome



Hyperglycemia also produces decreased nitric oxide levels

How common is the metabolic syndrome?

EPIDEMIOLOGY OF THE METABOLIC SYNDROME¹

ADULTS: 25% meet NCEP definition²

ADOLESCENTS: 4% meet NCEP definition³

- Metabolic syn.: can occur in children⁴

1. JAMA 1999, 282:1519, JAMA 2001, 286:1195

2. JAMA 2002, 287:356

3. Pediatric Research 2002, 51:131A

4. Diabetes Care 2001, 24:1359, Diabetes 2002, 51:204

METABOLIC SYNDROME IN CHILDREN OF VARIOUS ADIPOSITY

<u>Classification</u>	<u>Frequency</u>
Nonobese	0%
Overweight	0%
Moderately obese*	39%
Severely obese**	50%

* z score: 2.0-2.5; ** >2.5; NEJM 2004; 350:2362-74

What is the cause of the metabolic syndrome?

Cause of the metabolic syndrome

- insulin resistance --> direct actions
- compensation to IR --> indirect actions
(hyperinsulinism)

Causes of the metabolic syndrome

- insulin resistance --> direct actions

(+) rel. ins. def.: dysglycemia
 - IFG
 - IGT
 T2DM
 Incr. Tg (--> NAFL)
 Decr. HDL-C
 Dense LDL

Causes of the metabolic syndrome

- compensation to IR --> indirect actions

- Hyperinsulinism

- > atherogenesis (?)

- > Na⁺ retention --> Htn

- > melanocytes --> acanthosis nigricans

- > ovarian hyperandrogenism

- > hirsutism, PCOS

- > UA retention --> hyperuricemia

Consequence of the metabolic syndrome

- premature & accelerated atherogenesis

**How do we test for components
of the metabolic syndrome?**

Condition

Testing

Dysglycemia
T2DM

FBG/OGTT
“ “ “

Incr. Tg
Decr. HDL-C
Dense LDL

Lipid profile
“ “ “
infer from dx

NAFL

ALT

Hyperuricemia

uric acid (if symptomatic)

FPG (+/- OGTT)

Screen at age =>45 y/o

- BMI: <25 kg/M²: consider
- BMI: =>25 kg/M²: recommend

<45 y/o: overweight (+):

+ FHx for T2DM, Minority, GDM,
Htn, Decr. HDL-C, Incr. Tg,
previous abn GT (ADA)

FPG

Children: screening for T2DM

Age: \Rightarrow 10 y/o

Risk: Incr. BMI, Wt (+) \Rightarrow 2:

FHx + for T2DM

AN

Dyslipidemia

Minority

HTN

PCOS

Testing frequency: q 2 yr

Lipoprotein profile

Test every 5 years starting at 20 y/o
(NCEP ATP III)

follow per NCEP guidelines

**What are the possible outcomes
of NAFL?**

Possible outcomes of NAFL

- NASH (steatohepatitis)
- Cirrhosis
- Liver failure
- Hepatoma

Should plasma insulin be measured?

Yes - measure insulin

- increased insulin --> provides *objective* evidence of IR
- incr. insulin can be used to convince the *patient* that insulin resistance is present
- some definitions include biochemical demonstration of incr. insulin (AAACE)

No - do NOT measure insulin

- insulin assays from different manufacturers are NOT well standardized (lack of comparibility)
- difficult to achieve standard conditions
- most definitions do NOT include biochemical demonstration of incr. insulin
- adds expense

CONCLUSIONS / COMMENTARY

- 1) Obesity causes insulin resistance
- 2) Insulin resistance causes the metabolic syn.
- 3) Beta-cell decompensation ==> T2DM & other abn
- 4) Metabolic syndrome: highly atherogenic
- 5) Metabolic syndrome & T2DM occur in children & adolescents
- 6) Future prospects for a worldwide diabetes pandemic: *certain*