Insulin Resistance in Youth vs. Adults: From Physiology to Pathophysiology

Is the Glass Half Empty or Half Full?

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Insulin Sensitivity in Man

A state in which a given amount of insulin, exogenous or endogenous, produces a subnormal biological response:

- CHO
- Lipid
- Protein
Insulin Resistance in Youth

- Risk factors: Modifiable and Unmodifiable
- Induction of Insulin Resistance
- Alleviation of Insulin Resistance
- Youth-Adult Contrast in Insulin Sensitivity
Risk Factors for Insulin Resistance in Youth

- NAFLD, IUI, etc.
- Puberty
- T2DM
- Race
- PCOS
- Genetics
- Obesity
Risk Factors for Insulin Resistance in Youth

- NAFLD, IUI, etc.
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Longitudinal Study of Physiologic Insulin Resistance and Metabolic Changes of Puberty

**Insulin Sensitivity**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.8</td>
<td>15.3</td>
<td></td>
</tr>
</tbody>
</table>

p < 0.001

**Insulin Secretion**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.8</td>
<td>15.3</td>
<td></td>
</tr>
</tbody>
</table>

p < 0.005

**Fasting Insulin**

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.8</td>
<td>15.3</td>
<td></td>
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</tbody>
</table>

p = 0.023

Pediatr Res 60: 1, 2006
Adiponectin (\(\text{mg/ml}\))

<table>
<thead>
<tr>
<th>Age (yrs.)</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9.8</td>
<td>15.3</td>
</tr>
</tbody>
</table>

- Insulin sensitivity \(\downarrow\) by \(~50\%\)
- Insulin secretion doubled
- The \(\downarrow\) in insulin sensitivity was independent of changes in \% BF
- Adiponectin \(\downarrow\) by \(~50\%\)
- The ratio of Leptin/adiponectin \(\uparrow\) 5 fold.

Pediatr Res 60: 1, 2006
Longitudinal Study of Physiologic Insulin Resistance and Metabolic Changes of Puberty

- What causes pubertal insulin resistance?
- Does it involve protein and fat metabolism?
- What are the metabolic pathways responsible for it?
- Does pubertal IR have a teleological function?
Protein turnover during puberty in normal children

Correlations Between Fatty Acid and Glucose Metabolism
Potential Explanation of Insulin Resistance of Puberty

Testosterone Treatment in Adolescents with Delayed Puberty: Changes in Body Composition, Protein, Fat, and Glucose Metabolism

Dihydrotestosterone Treatment in Adolescents with Delayed Puberty: Does it Explain Insulin Resistance of Puberty?

Growth Hormone Treatment in Adolescent Males with Idiopathic Short Stature: Changes in Body Composition, Protein, Fat, and Glucose Metabolism
Pubertal insulin resistance involves protein and fat metabolism.

Pubertal IR is driven by GH and not gonadal sex steroids.

The ↑ in GH secretion during puberty leads to ↑ lipolysis and ↑ FFA ➔ to insulin resistance through the Randle cycle.

Pubertal IR and its compensatory hyperinsulinemia may serve to enhance growth and mass accretion.
Risk Factors for Insulin Resistance in Youth

- NAFLD, IUI, etc.
- T2DM
- PCOS
- Puberty
- Race
- Obesity
Hyperinsulinemia in African-American Children

Diabetes 51:3014, 2002

Insulin Sensitivity

Insulin Clearance

P = 0.021

P = 0.011
Are the black/white differences in insulin resistance and metabolic risks due to **biological differences** or **environmental differences** or both?

Arslanian S et al: Diabetes 51:3014, 2002
<table>
<thead>
<tr>
<th>Title</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Racial Differences in Adiponectin in Youth</td>
<td>2006</td>
</tr>
<tr>
<td>Ghrelin and Peptide YY in Youth: Are There Race-Related Differences?</td>
<td>2006</td>
</tr>
<tr>
<td>Lipolysis in African-American Children: Is It a Metabolic Risk Factor Predisposing to Obesity?*</td>
<td>2001</td>
</tr>
<tr>
<td>Fat Oxidation in Black and White Youth: A Metabolic Phenotype Potentially Predisposing Black Girls to Obesity</td>
<td>2008</td>
</tr>
<tr>
<td>Obesity, Regional Fat Distribution, and Syndrome X in Obese Black Versus White Adolescents: Race Differential in Diabetogenic and Atherogenic Risk Factors</td>
<td>2003</td>
</tr>
<tr>
<td>Whole-Body MRI and Ethnic Differences in Adipose Tissue and Skeletal Muscle Distribution in Overweight Black and White Adolescent Boys</td>
<td>2011</td>
</tr>
</tbody>
</table>
Adiponectin is ↓ in black youth.

Ghrelin (hunger hormone) suppression is ↓ in black youth.

PYY (satiety hormone) is ↓ in black youth.

Fat oxidation is ↓ in black female youth.

Visceral fat is ↓ in black youth despite similar BMI or total body fat.

Fat/CHO intake is ↑ in black youth’s diet, with inverse correlation to IS.

Diabetogenic risk is worse in black youth while atherogenic risk is worse in white youth.
Risk Factors for Insulin Resistance in Youth

- NAFLD, IUI, etc.
- Puberty
- Race
- T2DM
- PCOS
- Genetics
- Obesity
Healthy prepubertal black youth with +FH of T2DM have ~ 20% ↓ insulin sensitivity in the first decade of life.
Family History of T2DM: Impaired Insulin Sensitivity & β-cell Dysfunction in White Youth

Insulin Sensitivity (mg/kg/min per μU/ml) P=0.011

1st phase insulin (μU/ml) ns

Proinsulin (pmol/L) P=0.01

FH (-) FH (+)

FH (-) FH (+)

FH (-) FH (+)

FH (-) FH (+)

1000
800
600
400
200
0

P=0.008

200
400
600
800
1000
0
Risk Factors for Insulin Resistance in Youth

- NAFLD, IUI, etc.
- T2DM
- PCOS
- Puberty
- Race
- Genetics
- Obesity
Risk Factors for Insulin Resistance in Youth

- NAFLD, IUI, etc.
- Puberty
- Race
- T2DM
- PCOS
- Obesity
Insulin Sensitivity in Normal-weight & Obese Adolescents

**White**
- NW: 20.2 mg/min/Kg FFM per μl/ml
- OB: 35.2 mg/min/Kg FFM per μl/ml
- BMI: 22.9
- %BF: 43.4

**Black**
- NW: 21.2 mg/min/Kg FFM per μl/ml
- OB: 35.7 mg/min/Kg FFM per μl/ml
- BMI: 21.2
- %BF: 43.6

P < 0.001 for both groups
Relationship of BMI and % Body Fat to Insulin Sensitivity & Fasting Insulin

Insulin Sensitivity

Fasting Insulin

Fasting Insulin

Yellow: prepubertal, pink: pubertal

Arslanian S, 1998
Do ‘Apples’ Fare Worse Than ‘Pears’ in Youth?

Science 280: 1372, 1998
Abdominal Adipose Tissue (CT)

Lumbar L4-L5

Subcutaneous fat

Visceral fat
Insulin Sensitivity & Adiponectin in High vs. Low-VAT Obese Adolescents

**Insulin Sensitivity (mg/kg/min per µU/ml)**

- **High VAT**: P=0.032
- **Low VAT**:

**BMI 35.2**

% BF 43.4

**Adiponectin (µg/ml)**

- **High VAT**: P=0.05
- **Low VAT**

JCEM 88: 2534, 2003

Diabetes Care 2004
Correlation of VAT & SAT to Insulin Sensitivity & Fasting Insulin

- Glucose disposal (mg/kg/min)
- Fasting insulin (mU/ml)

Graphs showing the correlation between VAT and SAT with glucose disposal and fasting insulin, with a slope p<0.05.
Insulin Resistance

Link to the components of the metabolic syndrome and biomarkers of endothelial dysfunction in youth

Diabetes Care 30: 2091, 2007

Insulin Sensitivity Quartiles

Adiponectin

P < 0.01

Insulin Sensitivity Quartiles
Insulin Sensitivity Quartiles & Biomarkers of Endothelial Dysfunction

IL-6

P < 0.01

ICAM

P < 0.01

E-Selectin

P < 0.01

Insulin Sensitivity Quartiles

<25th 25-<50th 50-<75th >75th

(ng/ml)

IL-6

ICAM

E-Selectin

(ng/ml)
Question

Are all obese youth the same or have similar risk for T2DM or CVD?
Metabolically **Healthy** vs. **Unhealthy** Obese Youth

**Fat metabolically fit obese youth**

AGE: 13.2 yr  
BMI: 32.6 kg/m²  
% Body Fat: 42.6%  
W/H ratio: 0.86  
VAT: 60.0 cm²  
Insulin Sensitivity: 4.5 L

**Fat metabolically unfit obese youth**

AGE: 12.8 yr  
BMI: 33.2 kg/m²  
% Body Fat: 43.8%  
W/H ratio: 0.93  
VAT: 93.9 cm²  
Insulin Sensitivity: 1.7
Whole Body, Visceral Adiposity, and Liver Fat in Metabolically Healthy vs. Unhealthy Obese Youth

<table>
<thead>
<tr>
<th>Metric</th>
<th>MHO</th>
<th>MUHO</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat Mass (Kg)</td>
<td></td>
<td></td>
<td>P=NS</td>
</tr>
<tr>
<td>Visceral Adipose Tissue (cm²)</td>
<td></td>
<td></td>
<td>P=0.016</td>
</tr>
<tr>
<td>Liver Fat (%)</td>
<td></td>
<td></td>
<td>P=0.055</td>
</tr>
</tbody>
</table>
Adipokines & Inflammatory Markers in Metabolically Healthy vs. Unhealthy Obese Youth

Leptin/Adiponectin Ratio

- MHO: Lower
- MUHO: Higher

P < 0.004

hs-C-Reactive Protein

- MHO: Lower
- MUHO: Higher

P < 0.013
Type 2 Diabetes Risk in Metabolically Healthy vs. Unhealthy Obese Youth

Hepatic Insulin Sensitivity

Peripheral Insulin Sensitivity

β-cell Function Relative to IS

P<0.0001

P=0.021
Atherogenic Lipoprotein Concentrations in Metabolically Healthy vs. Unhealthy Obese Youth

Very Small LDL

Small HDL

Large VLDL

P = 0.035

P = 0.021
Take Home Message

Not all obese youth are the same

Metabolically healthy obese youth have more favorable risk profile than metabolically unhealthy youth despite similar BMI and total body fat.
Risk Factors for Insulin Resistance in Youth

- Race
- Genetics
- PCOS
- T2DM
- NAFLD, IUI, etc.
- Puberty
- Race
- Genetics
- Obesity

Checkmarks indicate factors associated with insulin resistance in youth.
Insulin Sensitivity in Adolescents with PCOS


Glucose Disposal (mg/kg/min)

- Control
- PCOS

PCOS
Control

<table>
<thead>
<tr>
<th></th>
<th>PCOS</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>12.0 ± 0.7</td>
<td>12.1 ± 0.6</td>
</tr>
<tr>
<td>Free T. (pg/ml)</td>
<td>7.2 ± 1.4</td>
<td>3.4 ± 1.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.1 ± 1.8</td>
<td>31.4 ± 1.3</td>
</tr>
<tr>
<td>% Body Fat</td>
<td>43.2 ± 1.4</td>
<td>45.6 ± 1.1</td>
</tr>
<tr>
<td>FM (kg)</td>
<td>34.8 ± 2.9</td>
<td>34.0 ± 2.2</td>
</tr>
<tr>
<td>TAF (cm²)</td>
<td>546 ± 49</td>
<td>484 ± 44</td>
</tr>
</tbody>
</table>
Risk Factors for Insulin Resistance in Youth

- NAFLD, IUI, etc.
- Puberty
- Race
- PCOS
- Genetics
- Obesity
- T2DM
Youth Type 2 Diabetes

Insulin resistance, β-cell failure, or both?

Diabetes Care 28: 638, 2005
Ominous Octet

- β-cell Failure
- Glucagon & α-cell Dysfunction
- Hepatic Insulin Resistance
- Increased hepatic glucose production
- Neurotransmitter dysfunction

Decreased incretin effect

- Increased glucagon secretion
- Impaired insulin secretion

Hyperglycaemia

- Lipolysis & Adipose Insulin Resistance
- Peripheral Insulin Resistance

Diabetes 58: 773, 2009
Insulin Resistance in Youth

- Risk factors: Modifiable and Unmodifiable
- Induction of Insulin Resistance
- Alleviation of Insulin Resistance
- Youth-Adult Contrast in Insulin Sensitivity
Our objective was to create an acute model of lipotoxicity, and assess how quickly we can induce insulin resistance and ectopic fat deposition in youth.
Insulin Sensitivity in Response to FFA Elevation in Prepubertal Youth

Paired experiments of NS vs. 20% IL infusion for 3 hrs. followed by a 2hr. hyperglycemic clamp

FFA: $\uparrow$ from ~ 0.21 to 0.61 mmol/L
Effect of Intralipid Infusion on Hepatic & Peripheral Insulin Sensitivity in Healthy Normal-Weight Adolescents (2013)

Hepatic Insulin Sensitivity

Peripheral Insulin Sensitivity

(P<0.01)

Intralipid

30%↓

Intralipid

39%↓

(2013)
Effect of Intralipid Infusion on Fasting Glucose & Insulin in Healthy Normal-Weight Adolescents

Fasting Insulin

<table>
<thead>
<tr>
<th></th>
<th>NS</th>
<th>Intralipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>μU/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>57%</td>
<td></td>
</tr>
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</table>

Fasting Glucose

<table>
<thead>
<tr>
<th></th>
<th>NS</th>
<th>Intralipid</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>4%</td>
<td></td>
</tr>
</tbody>
</table>
Effect of Intralipid Infusion on Intramyocellular Lipid (IMCL) in Healthy Normal-Weight Adolescents

Intramyocellular Lipid by $^1$H-MR Spectroscopy

![Graph showing effect of Intralipid infusion on IMCL.](image)

- NS vs. Intralipid: P < 0.01
- Intralipid increases IMCL by 85%
Insulin Resistance in Youth

- Risk factors: Modifiable and Unmodifiable
- Induction of Insulin Resistance
- Alleviation of Insulin Resistance
- Youth-Adult Contrast in Insulin Sensitivity
Lipid Overflow Theory

- Energy intake
  - Physical activity
  - Sedentary time
  - Vigorous exercise

Positive energy balance

- Saturated expansion of adipose tissue
- Inability of subcutaneous adipose tissue to expand (e.g., lipodystrophies)

LIPID OVERFLOW

- Visceral adiposity
- Liver fat
- Epiphenotypic visceral fat
- Muscle fat
- Renal medullary fat
- Pancreatic fat

Insulin resistance/inflammation

- Increased cardiometabolic risk
- Impaired insulin secretion
- High risk of type 2 diabetes

Physiol Rev 93: 359, 2013
Effects of Aerobic Versus Resistance Exercise Without Caloric Restriction on Abdominal Fat, Intrahepatic Lipid, and Insulin Sensitivity in Obese Adolescent Boys: A Randomized, Controlled Trial

Diabetes 61: 1-9, 2012

3 m. exercise training
3x/week, 60 min/session
no calorie restriction
Average Wt. 100 Kg

C

Insulin sensitivity
(mg/FFM·kg/min per μU/ml)

Control
(13)

Aerobic
(16)

Resistance
(16)

27% ↑
P=0.015

Average Wt. 100 Kg
Effects of Aerobic Versus Resistance Exercise Without Caloric Restriction on Abdominal Fat, Intrahepatic Lipid, and Insulin Sensitivity in Obese Adolescent Boys
A Randomized, Controlled Trial

Diabetes 61: 1-9, 2012
Insulin Resistance in Youth

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Treatment Options for type 2 Diabetes in Adolescents and Youth

Overall Failure rate 45.6%
Metformin Failure rate 51.7%
Met + Rosi Failure rate 38.6%

Designed in 2002, ended 2/2011, results April 2012
Metformin failure Rate in T2DM

**Adults vs. Youth**

- **1 yr**: 10% failing Metformin Rx
- **2 yrs**: 20% failing Metformin Rx
- **5 yrs**: 50% failing Metformin Rx

**Failure Definition**

- TODAY: HbA1c > 8% x 6m
- ADOPT: FG > 180 mg/dl x 2.

Kahn et al for ADOPT study, NEJM 2006
Zeitler et al for TODAY study, NEJM 2012
Metformin + Rosi Failure Rate in T2DM

Adults vs. Youth

% Failing Treatment

TODAY: HbA1c >8% x 6m
DOD: Start of Insulin

Rascati et al Diabetes, Obesity & Metabolism 2013
Zeitler et al for TODAY study, NEJM 2012
Natural History of Type 2 Diabetes

Figure 6: Natural history of type 2 diabetes and possible inadequacies of the standard therapeutic approach

Lancet June 25, 2011
Youth Type 2 Diabetes

One or more of the pathophysiological mechanisms of type 2 diabetes is worse in youth compared with adults.
Insulin sensitivity across the lifespan from obese adolescents to obese adults with impaired glucose tolerance: Who is worse off?

Pediatric Diabetes 2017

**Insulin Sensitivity**

![Graph showing insulin sensitivity comparison between youth and adults.](image)

**Fasting Insulin**

![Graph showing fasting insulin comparison between youth and adults.](image)

- Youth: P<0.0001
- Adults: P<0.0001
Insulin sensitivity across the lifespan from obese adolescents to obese adults with impaired glucose tolerance: Who is worse off?

Pediatric Diabetes 2017

Hepatic Glucose Production

Hepatic Insulin Sensitivity

P<0.0001

P=0.002
Tack