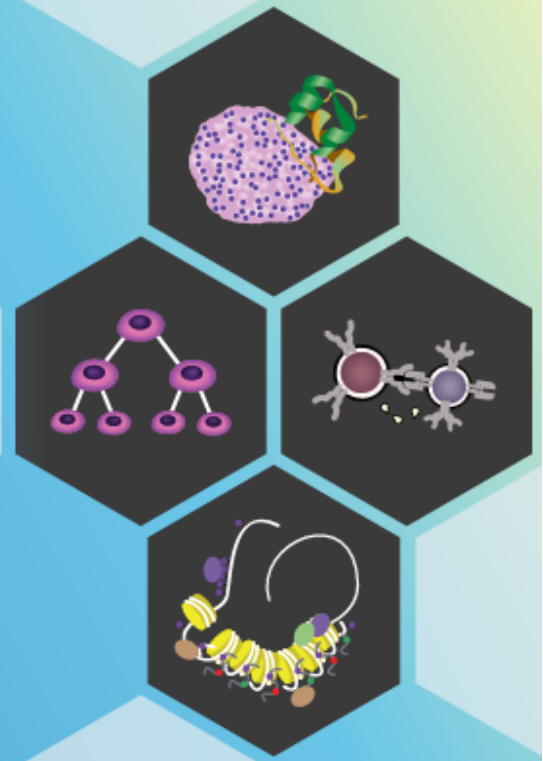
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

# Youth-Onset Type 2 Diabetes: Amplified Pathology due to Hormonal, Genetic, Environmental and Societal Influences

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# Disclosures

- Grant/Research Support from Eli Lilly, Inc., and Novo Nordisk.
- Consultant for Eli Lilly, Inc.

*This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.*

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

*This presentation has been peer-reviewed and no conflicts were noted.*

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

**STATE LAW:**

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

***EXEMPTION:***

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

***The following CLC & IB components will be addressed in this presentation:***

- *Race/ethnicity-based inequities in the clinical care of children and adolescents. Social determinants of health as a risk factors for youth-onset type 2 diabetes. Inequities in the clinical care of immigrant youth with type 2 diabetes.*
- *Body size and race.*

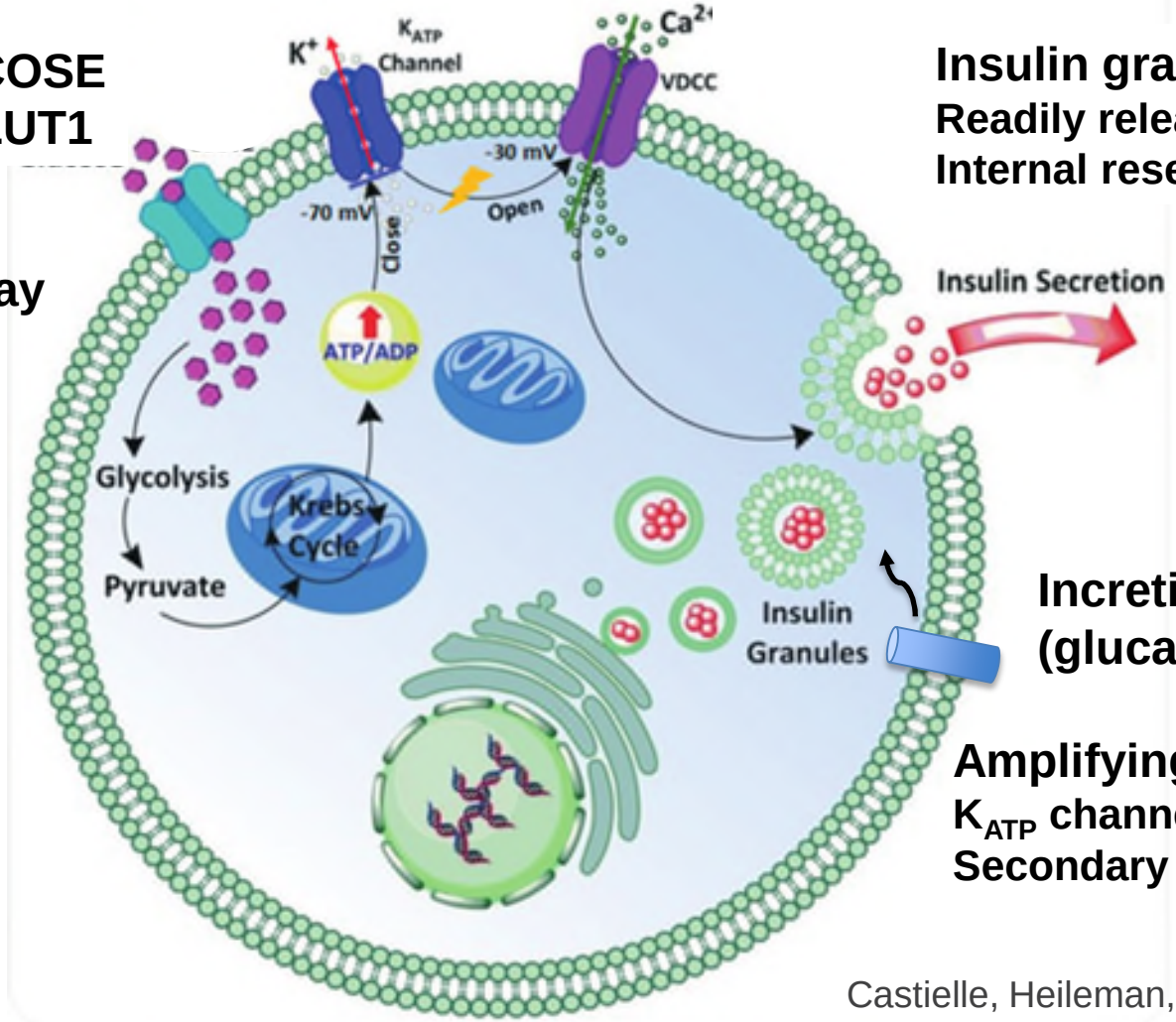
# Outline

- Pathophysiology of T2D – insulin secretion, insulin response, β-cell failure
- Glucose homeostasis during puberty
- Physiologic differences in youth-onset and adult-onset T2D
- Pathogenic genetic risk factors
- Environmental and societal factors
- Precision-based targets for prevention and therapy

# β-cell Glucose-Stimulated Insulin Secretion

**ATP-sensitive K channel is closed; membrane depolarization; Ca2+ channel opens**

**GLUCOSE**
**GLUT1**




**Insulin granule exocytosis**
**Readily releasable pool (1st + 2nd phase)**
**Internal reserve pool (2nd phase)**

**Triggering pathway**
**Glucokinase**

**GK and the $K_{ATP}$ regulate first-phase insulin secretion**

**Incretin Receptors (glucagon, GLP-1, GIP)**

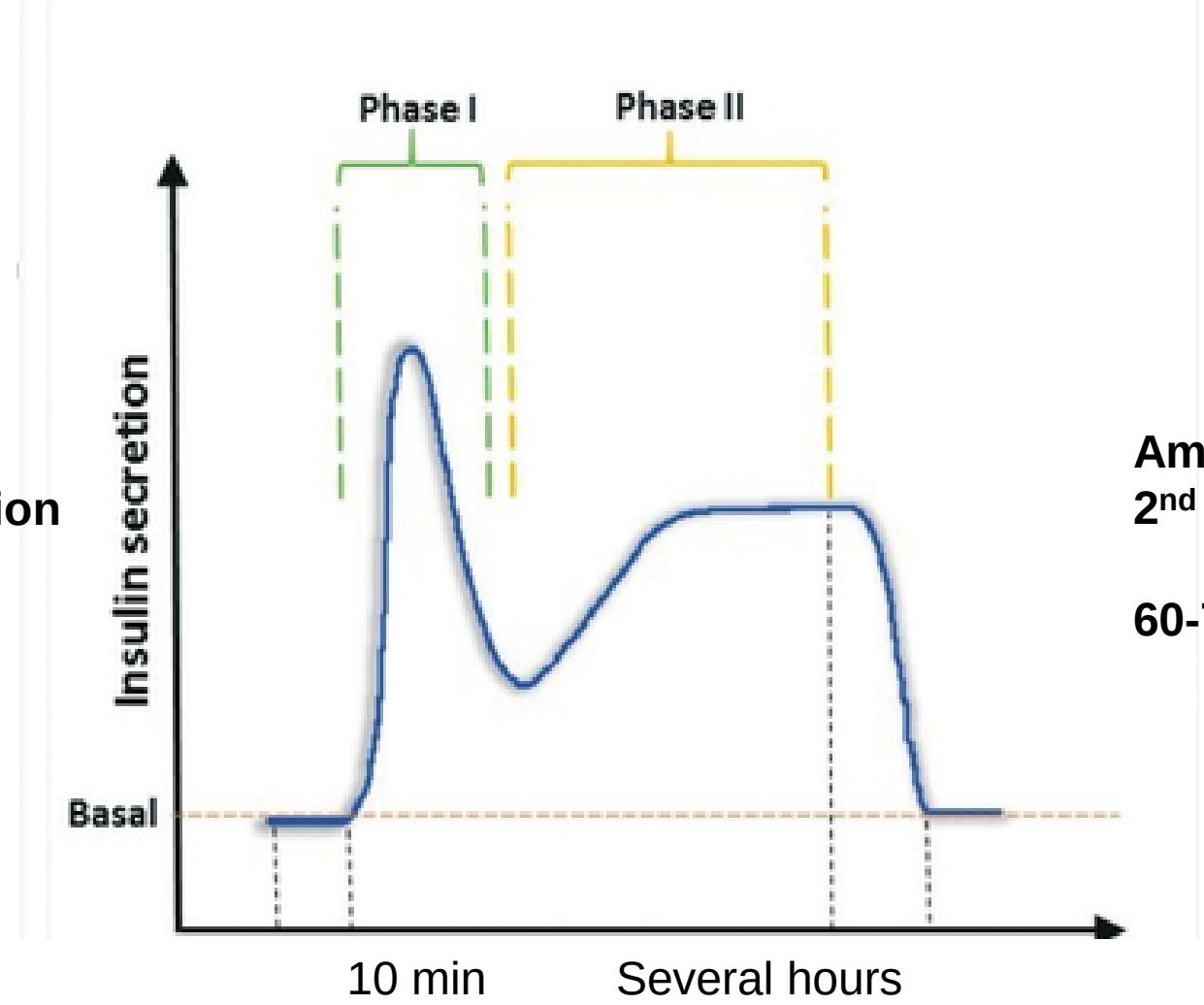
**Amplifying pathway**
**$K_{ATP}$ channel-independent glc sensing**
**Secondary stimuli (2nd phase)**

Castielle, Heileman, Tabrizian. Lab Chip 2016;16:409.

# Glucose-Stimulated Insulin Secretion

**Triggering pathway:**
**1st phase insulin secretion**

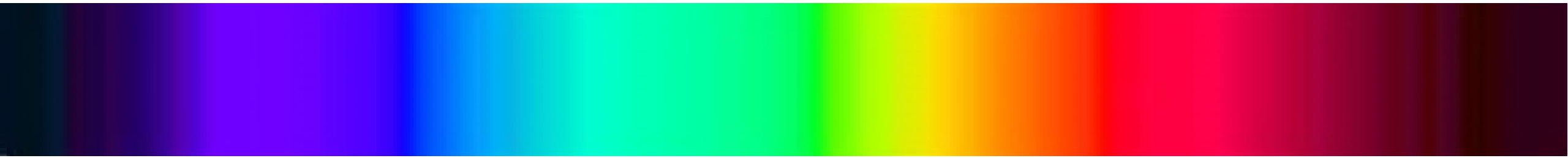
**30-40% of total insulin secretion**




**Amplifying pathway:**
**2nd phase insulin secretion**

**60-70% of total insulin secretion**

# Mechanisms of β-Cell Failure in Type 2 Diabetes



Insulin resistance  Insulin Secretion  IGT  IFG  β-cell failure  Diabetes

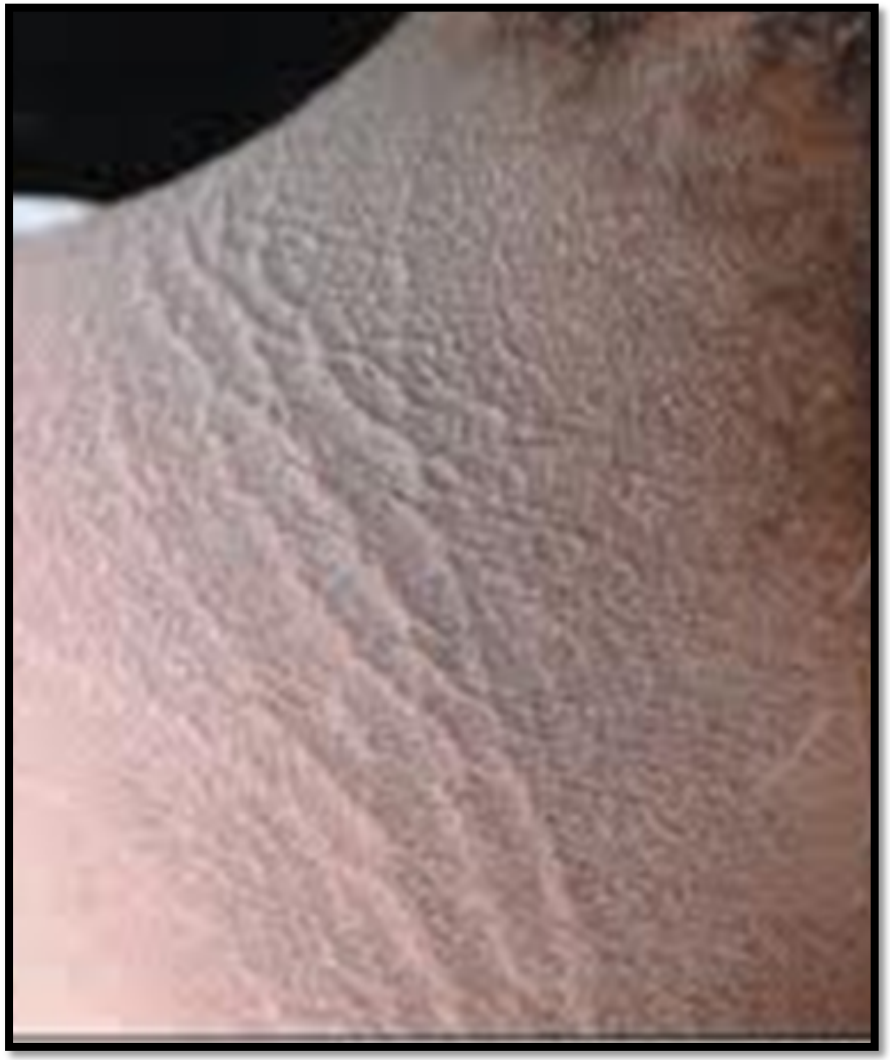
**OBESITY**
**PUBERTY**

**GENETICS**
**METABOLIC STRESS**

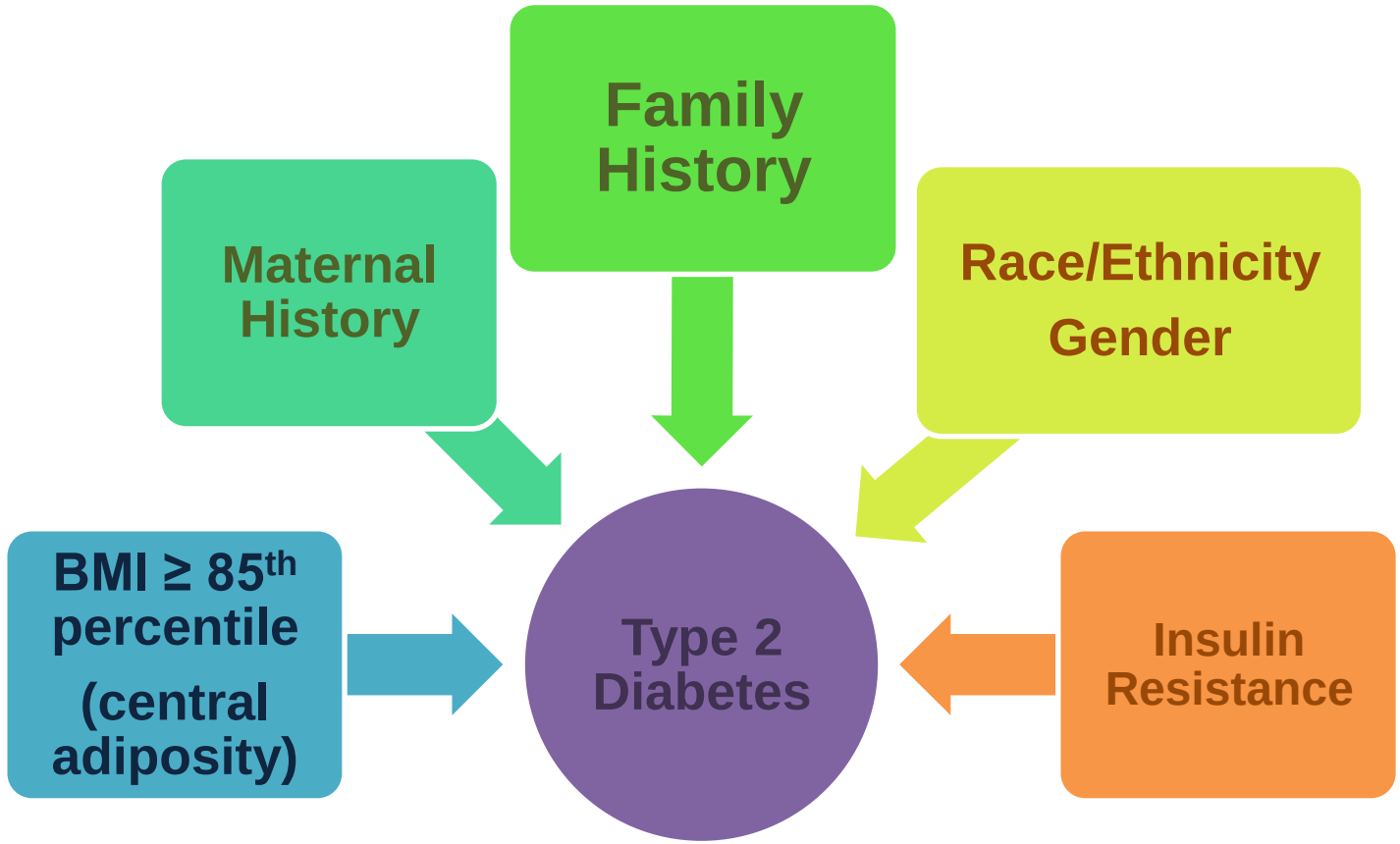
**DETERIORATION OF β-CELL FUNCTION IN THE FACE OF MULTIPLE PHYSIOLOGIC STRESSORS**

# Case History – 12 yo

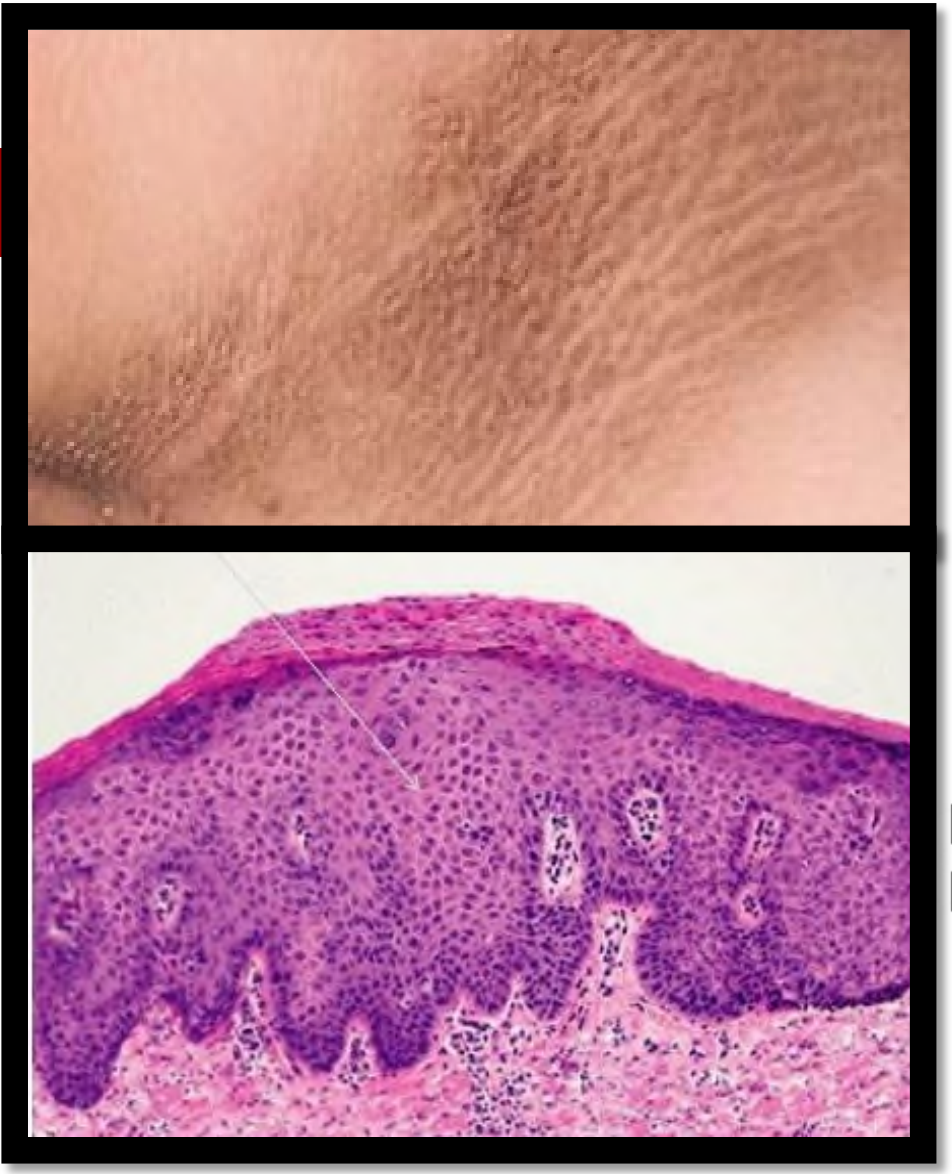
- Increasing BMI
- Maternal grandparents with T2D (dx in 60’s)
- Mother with GDM during recent pregnancy
- Increasing acanthosis nigricans
- Irregular, heavy menses
- More frequent headaches
- HbA1C 6.1%; 2-hour OGTT PG 178

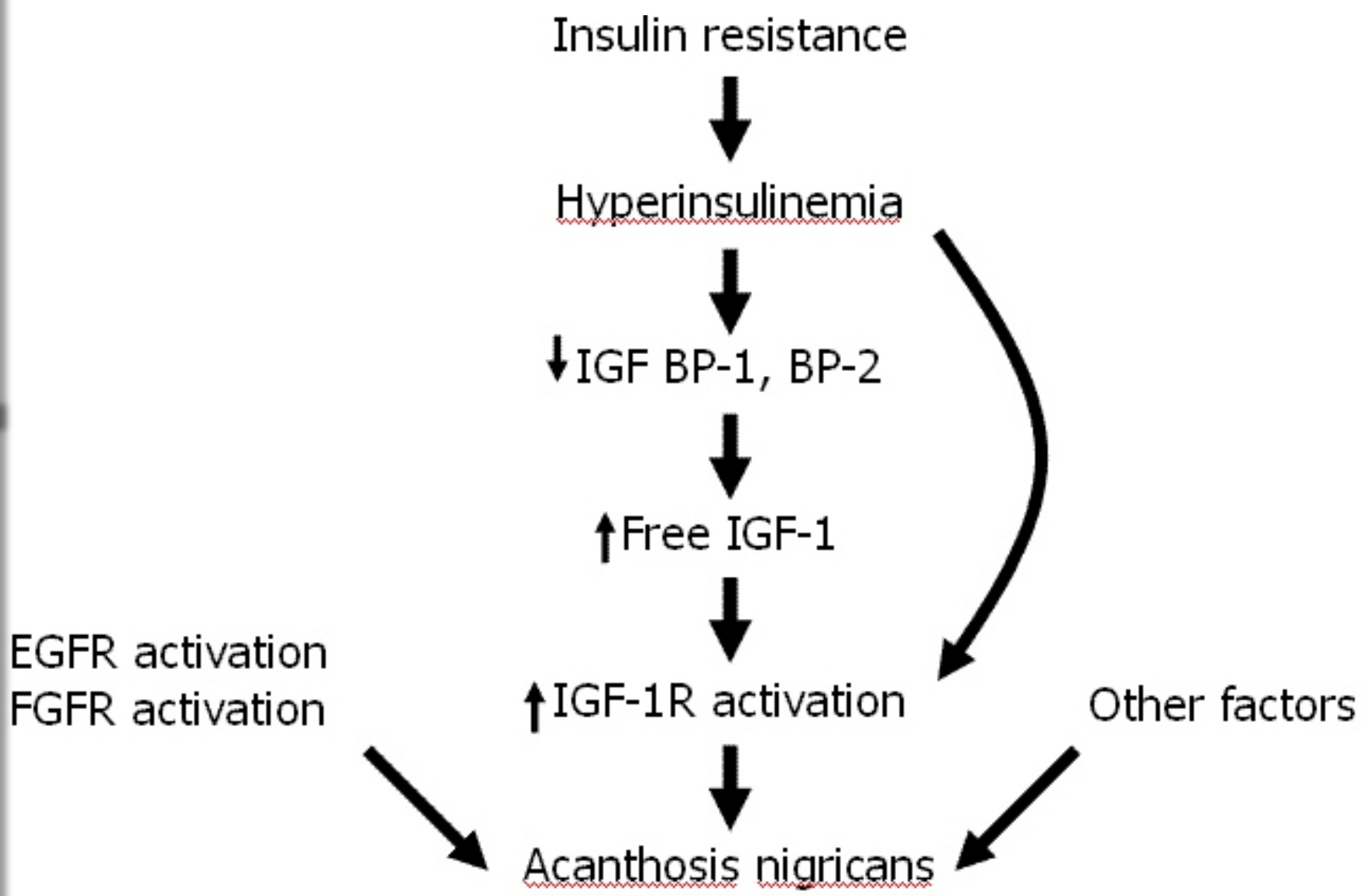


# Risk Factors for Youth-onset Type 2 Diabetes



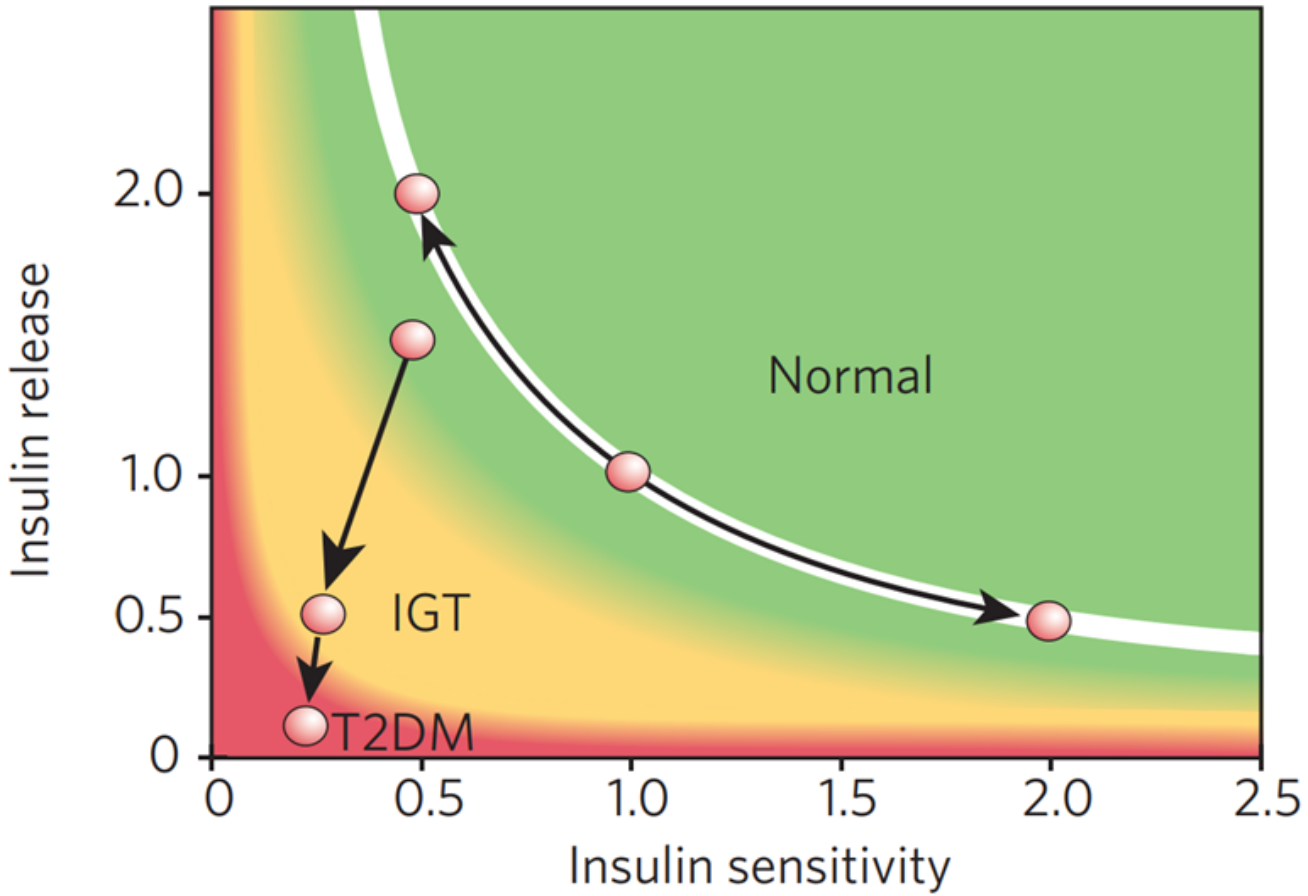

Hitt TA, Hannon TS, Magge SN. *J Clin Endocrinol Metab* 2023.






**proliferation of epidermal keratinocytes and dermal fibroblasts**

# Relationship of Insulin Sensitivity and Insulin Release



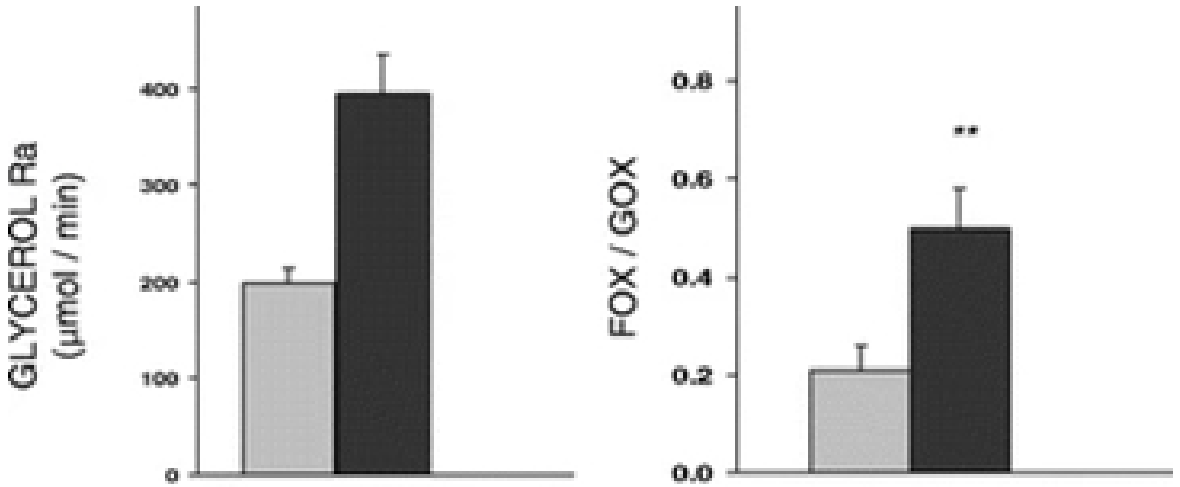

Kahn SE et al. Nature 2006;444:840.

# Markers for Risk for T2D Increase During Puberty in Lean Adolescents




Hannon, Arslanian. *Pediatr Res* 2006.

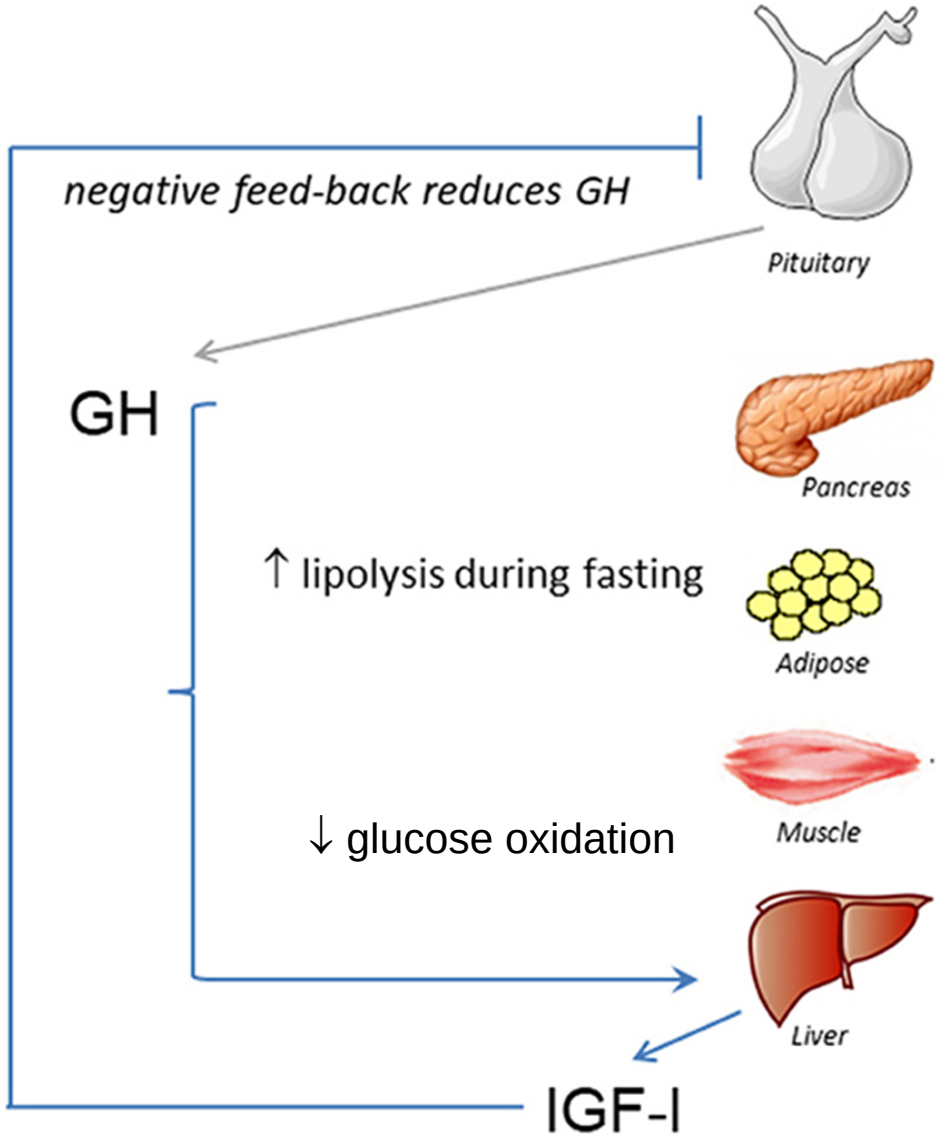
# Longitudinal Study of Substrate Utilization During Normal Puberty in Lean Adolescents




Before Puberty
During Puberty

Hannon, Arslanian. *Pediatr Res* 2006.

# GH is directly associated with insulin resistance, increased lipolysis during normal puberty



# RISE CONSORTIOM

To identify approaches that can preserve or improve β-cell function in youth and adults with dysglycemia.

## Proof-of-Principle Studies

### Comparing medications

- Pediatric Medication Study (10-19 years)
- Adult Medication Study (20-65 years)

# RISE Inclusion Criteria

| Criteria | Pediatric Medication | Adult Medication | Adult Surgery |
|---|---|---|---|
| Age (years) | 10-19 | 20-65 | 22-65 |
| Tanner stage | 2 or above | | |
| Body mass index | ≥85$^{th}$ %ile but ≤50 kg/m$^2$ | 25-50 kg/m$^2$ | 30-40 kg/m$^2$ |
| Fasting glucose | ≥90 mg/dL | 95-125 mg/dL | ≥90 mg/dL |
| 2-hour OGTT glucose | ≥140 mg/dL | ≥140 mg/dL | ≥140 mg/dL |
| Diabetes duration | <6 months | <1 year | |
| Diabetes medication status | Metformin <6 months<br>Insulin <2 weeks | Naïve | |
| HbA1c | ≤8.0% (drug naïve)<br>≤7.5% (on metformin <3 months)<br>≤7.0% (on metformin 3-6 months) | ≤7.0% | |

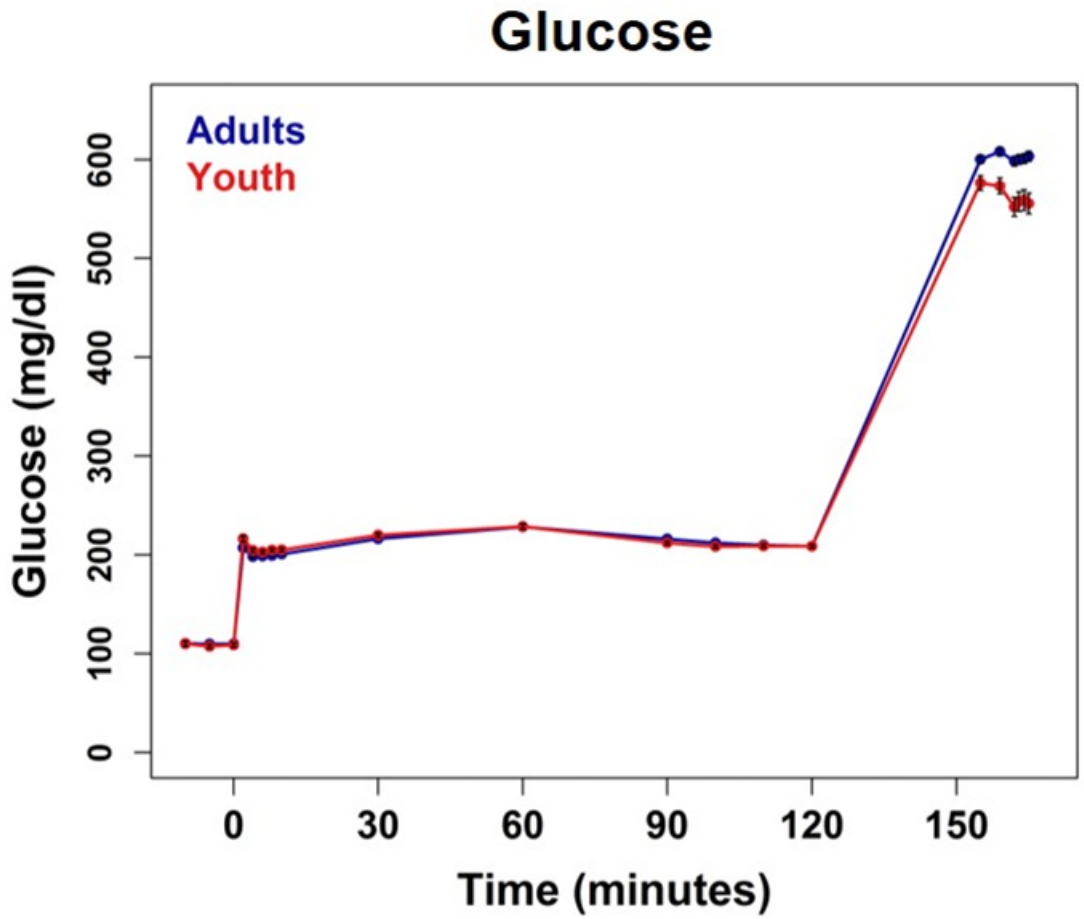
The RISE Consortium: Diabetes Care 37:780-788; 2014.

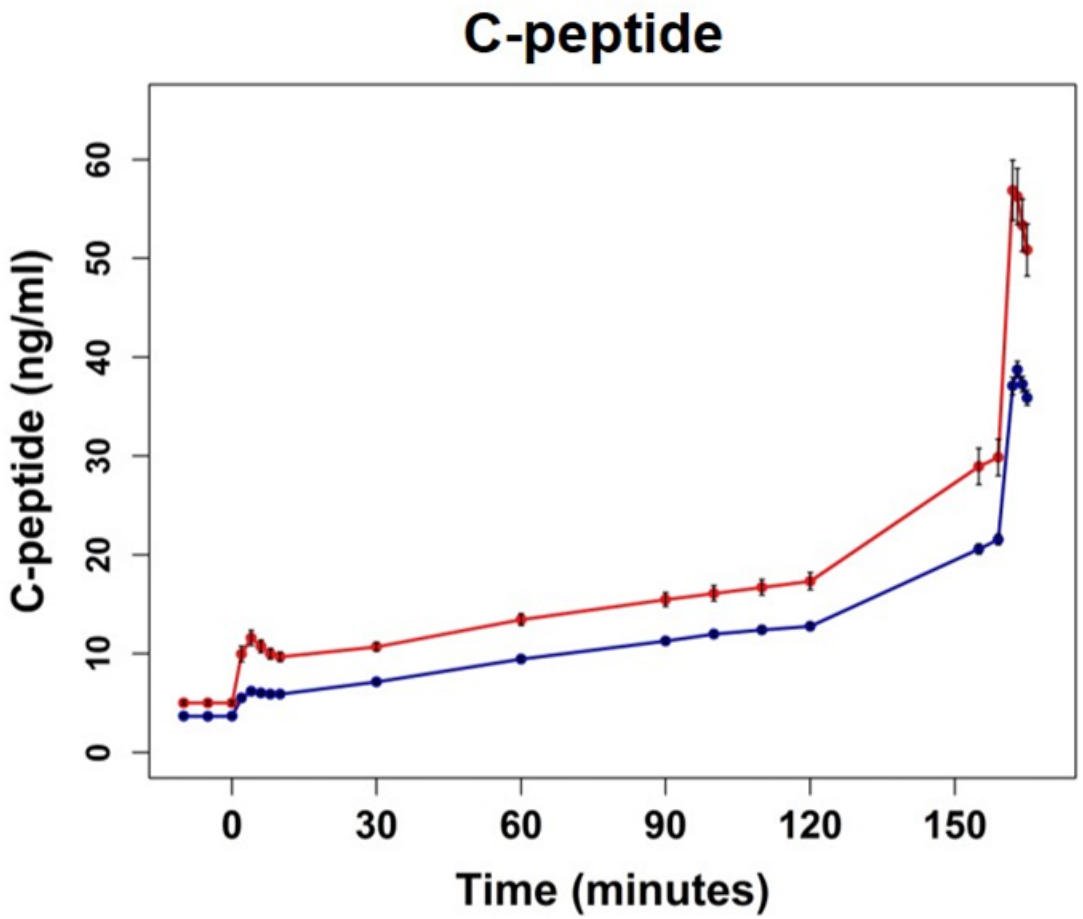
# RISE Baseline Characteristics

| Criteria | Pediatric | Adult Med |
|---|---|---|
| Number of participants | 91 | 267 |
| Age (y) | 14 ± 2 * | 54 ± 9 |
| Female (n, %) | 64 (71) * | 114 (43) |
| Weight (kg) | 100 ± 24 | 102 ± 20 |
| BMI (kg/m$^2$) | 37 ± 6 * | 35 ± 6 |
| Fasting glucose (mg/dL) | 108 ± 17 * | 111 ± 11 |
| 2-hour glucose (mg/dL) | 184 ± 47 | 182 ± 41 |
| Fasting insulin (µU/mL) | 31 (10, 95) * | 14 (5, 43) |

*p<0.05 across studies
Data are mean±SD or geometric mean (95% CI) for non-normally distributed variables

# Pre-treatment Differences between Youth and Adults



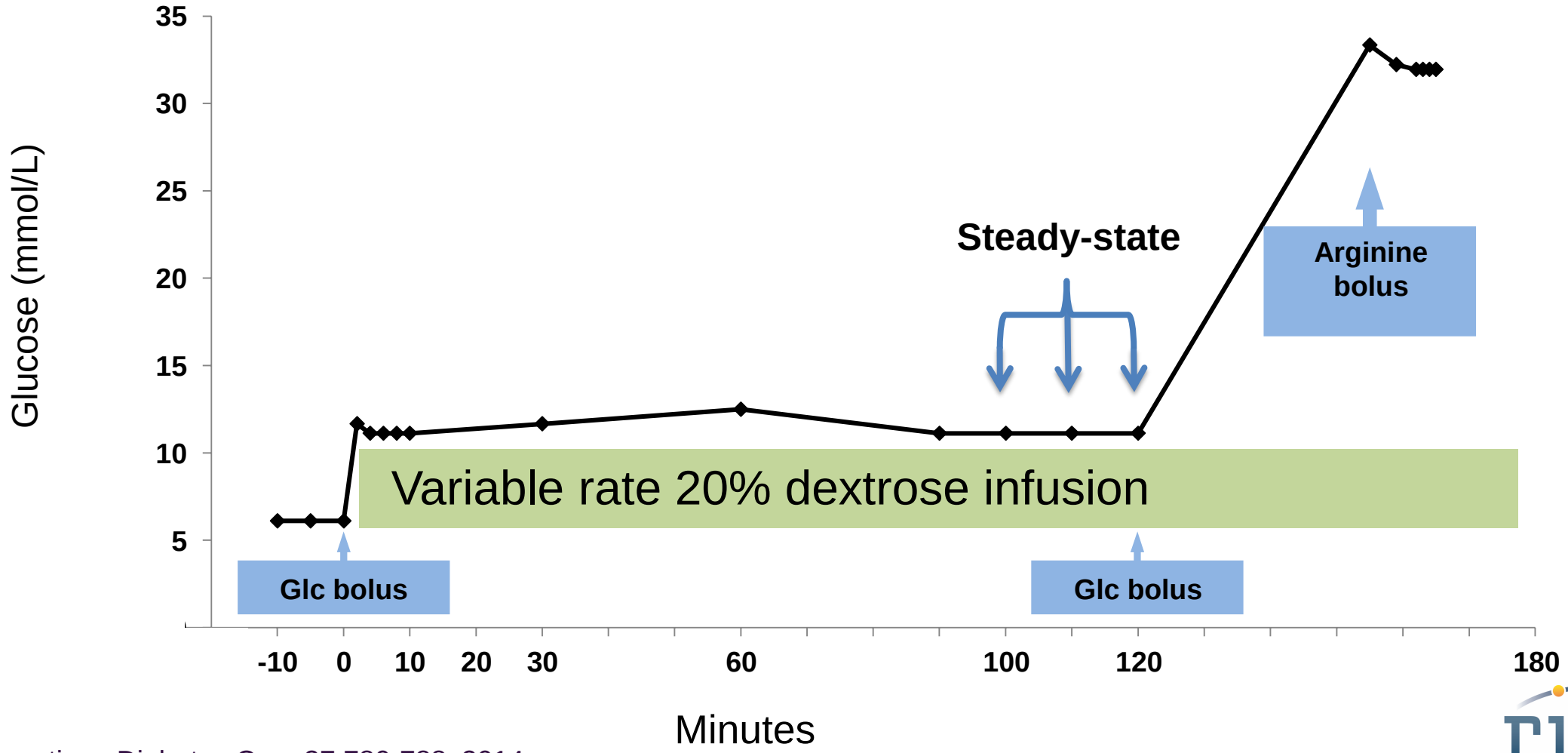

The RISE Consortium. Diabetes Care 2018;41:1696.

# RISE Randomized Study Interventions

| **Pediatric Medication** | **Adult Medication** |
|---|---|
| Metformin | Metformin (blinded) |
| Glargine → Metformin | Glargine → Metformin |
| | Liraglutide + Metformin |
| | Placebo (blinded) |

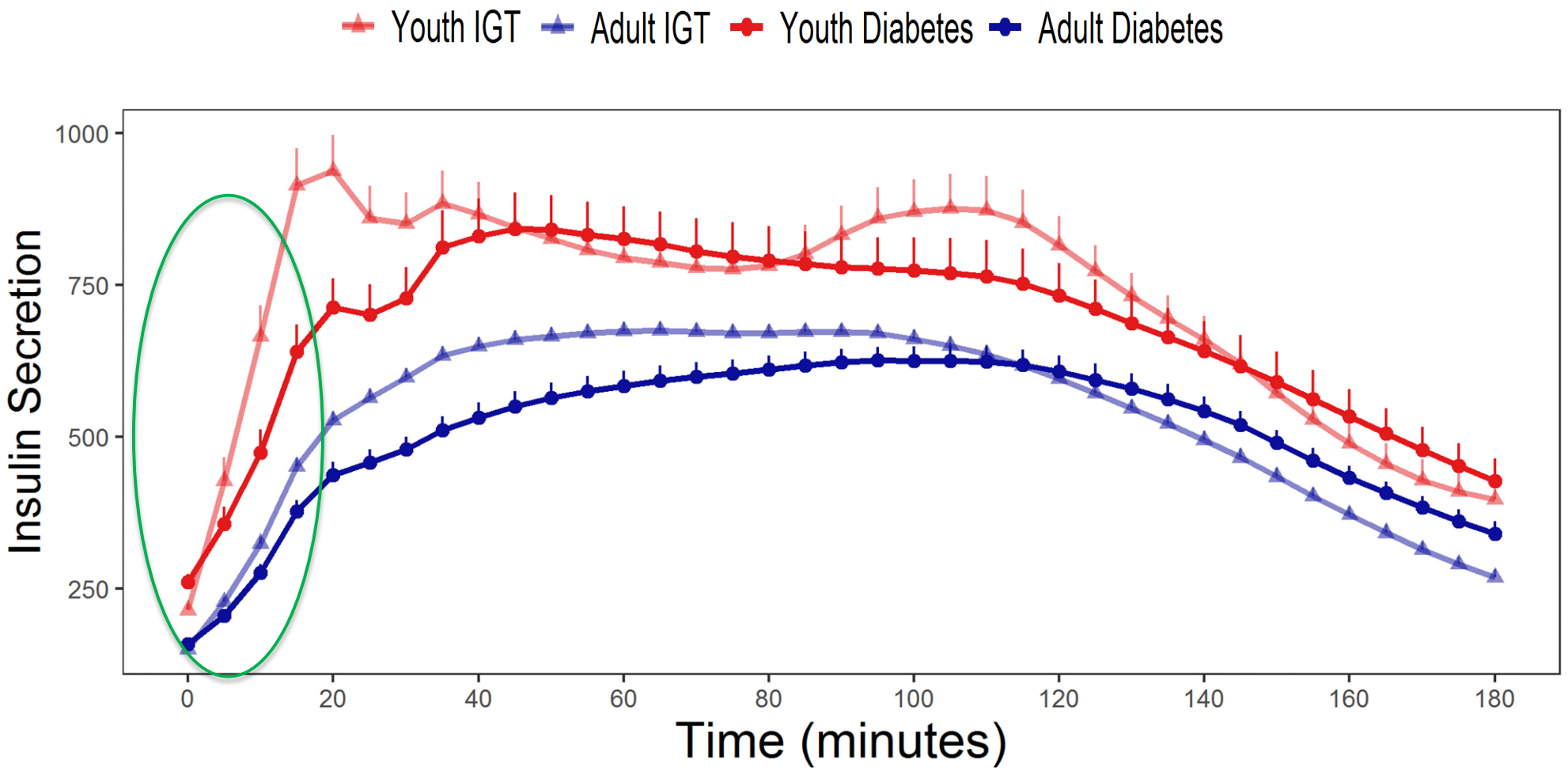
The RISE Consortium: Diabetes Care 37:780-788; 2014

# Two-step Hyperglycemic Clamp Protocol




The RISE Consortium: Diabetes Care 37:780-788; 2014

# Modeled Insulin Secretion during OGTT in Youth and Adults




Utzschneider KM, The RISE Consortium: Diabetes Care. Vol 44:817, 2021

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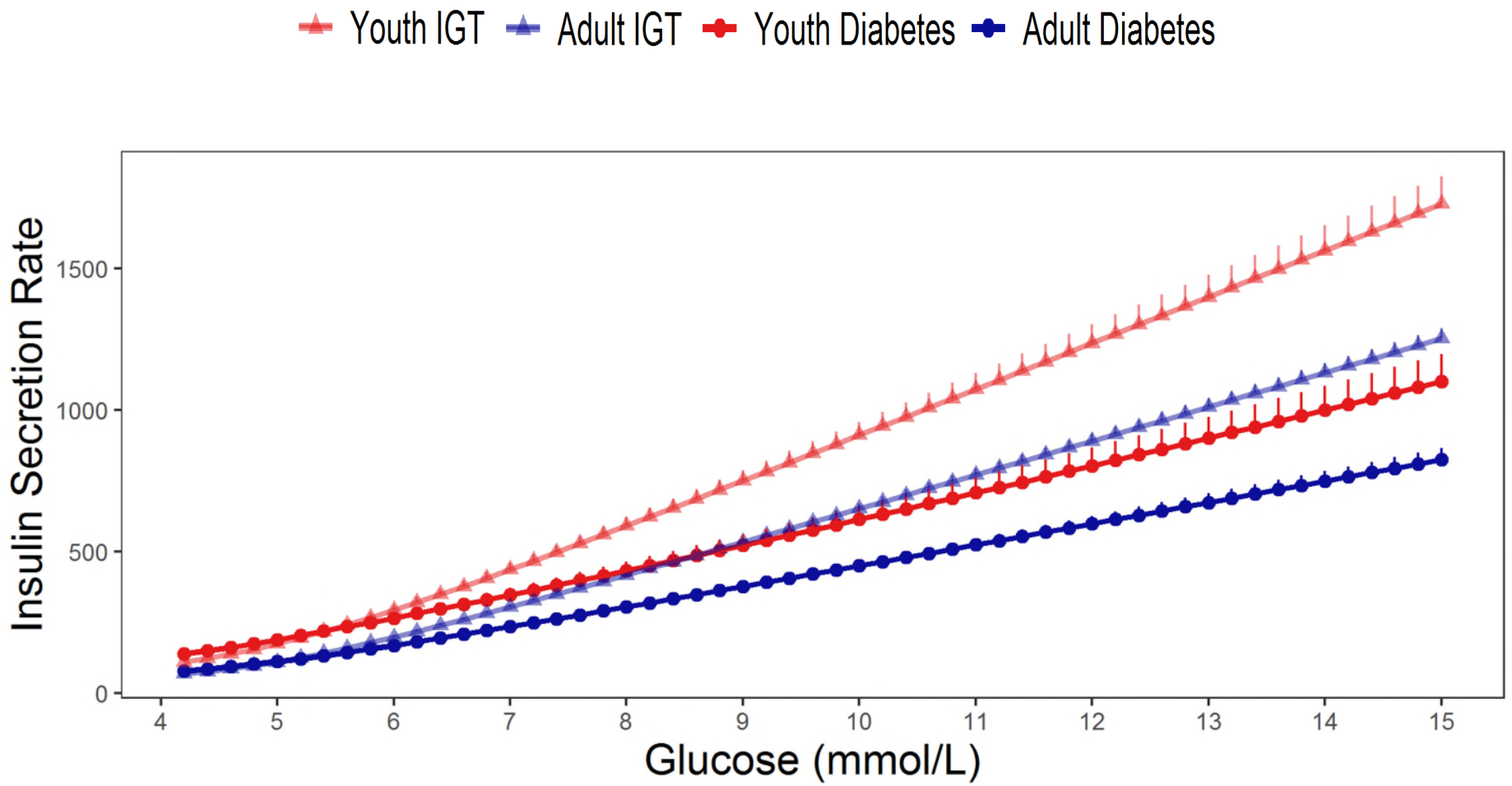


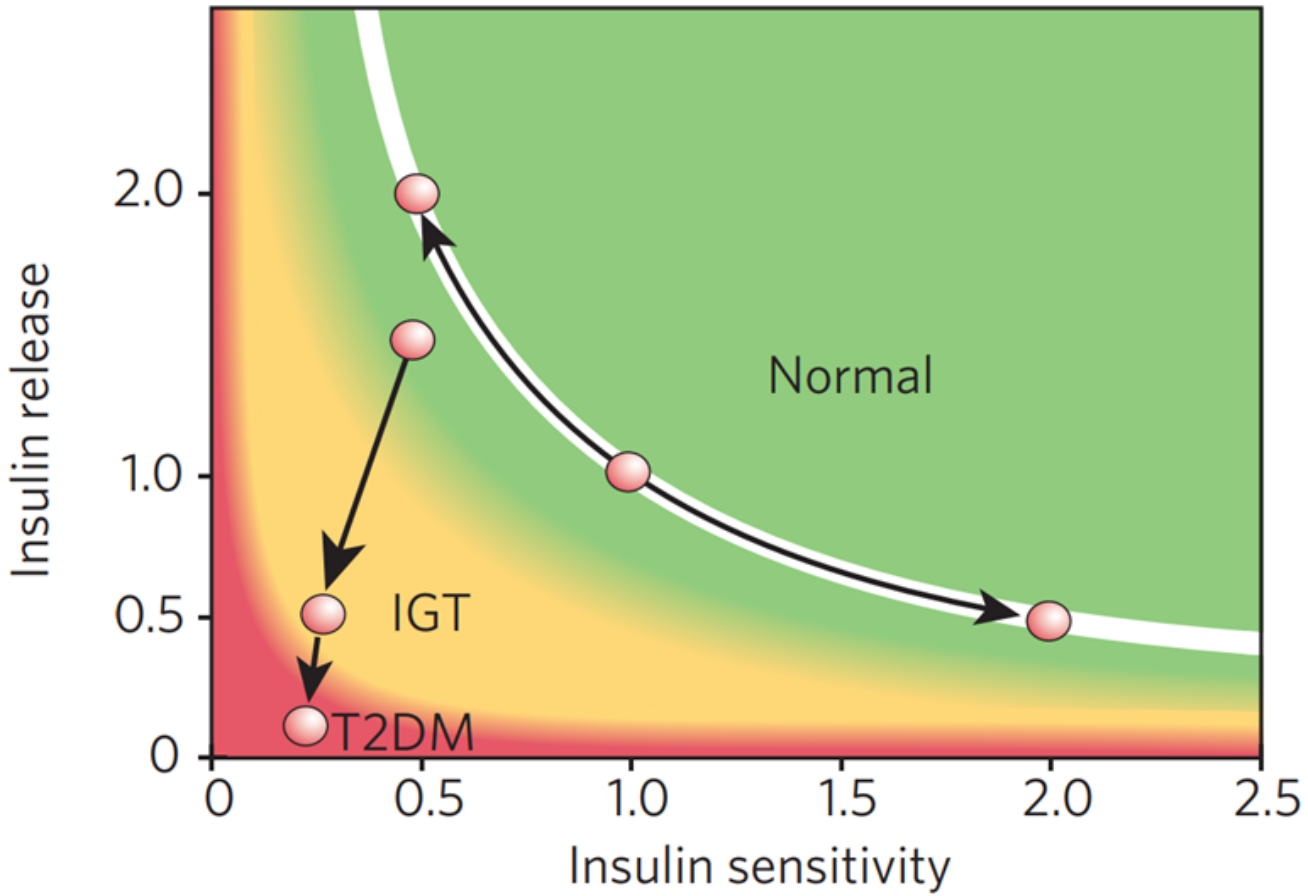

Utzschneider KM, The RISE Consortium: Diabetes Care. Vol 44:817, 2021

# RISE Randomized Study Interventions

| **Medications** |
| --- |
| Metformin (2000 mg/day) for 12 months |
| Glargine (titrated to FPG <90 mg/dL for 3 months<br>→ Metformin (2000 mg/day) for 9 months |
| Medications Stopped at 12 month visit for 3-month wash-out |

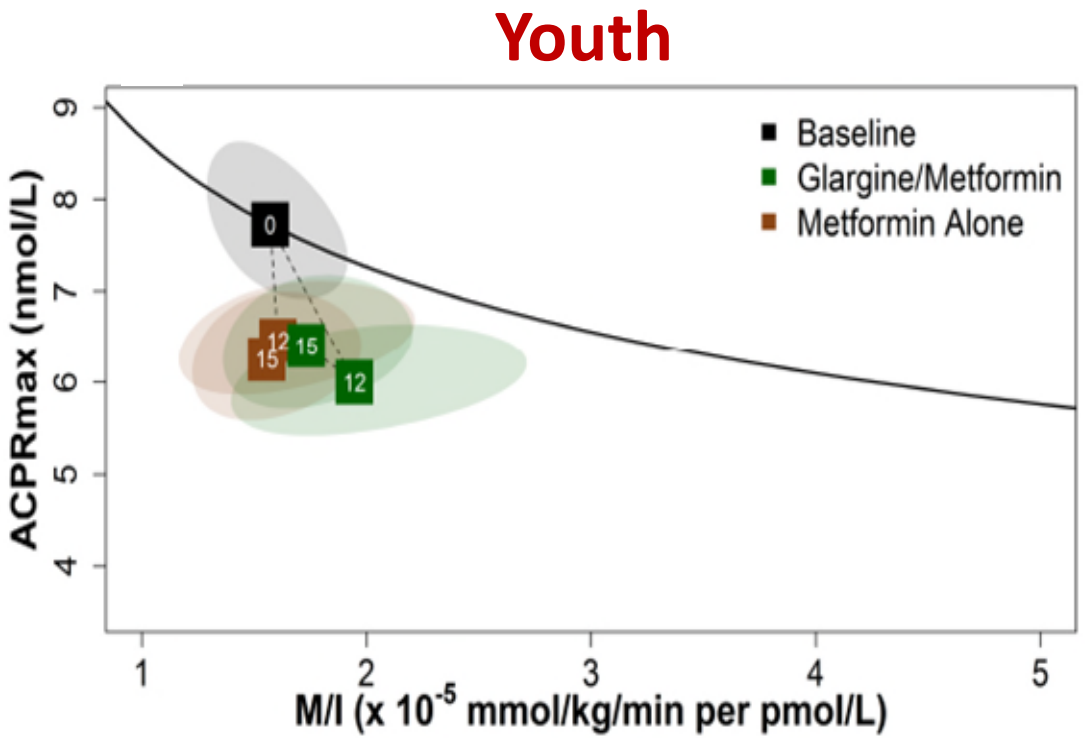
The RISE Consortium: Diabetes Care 37:780-788; 2014

# Relationship of Insulin Sensitivity and Insulin Release



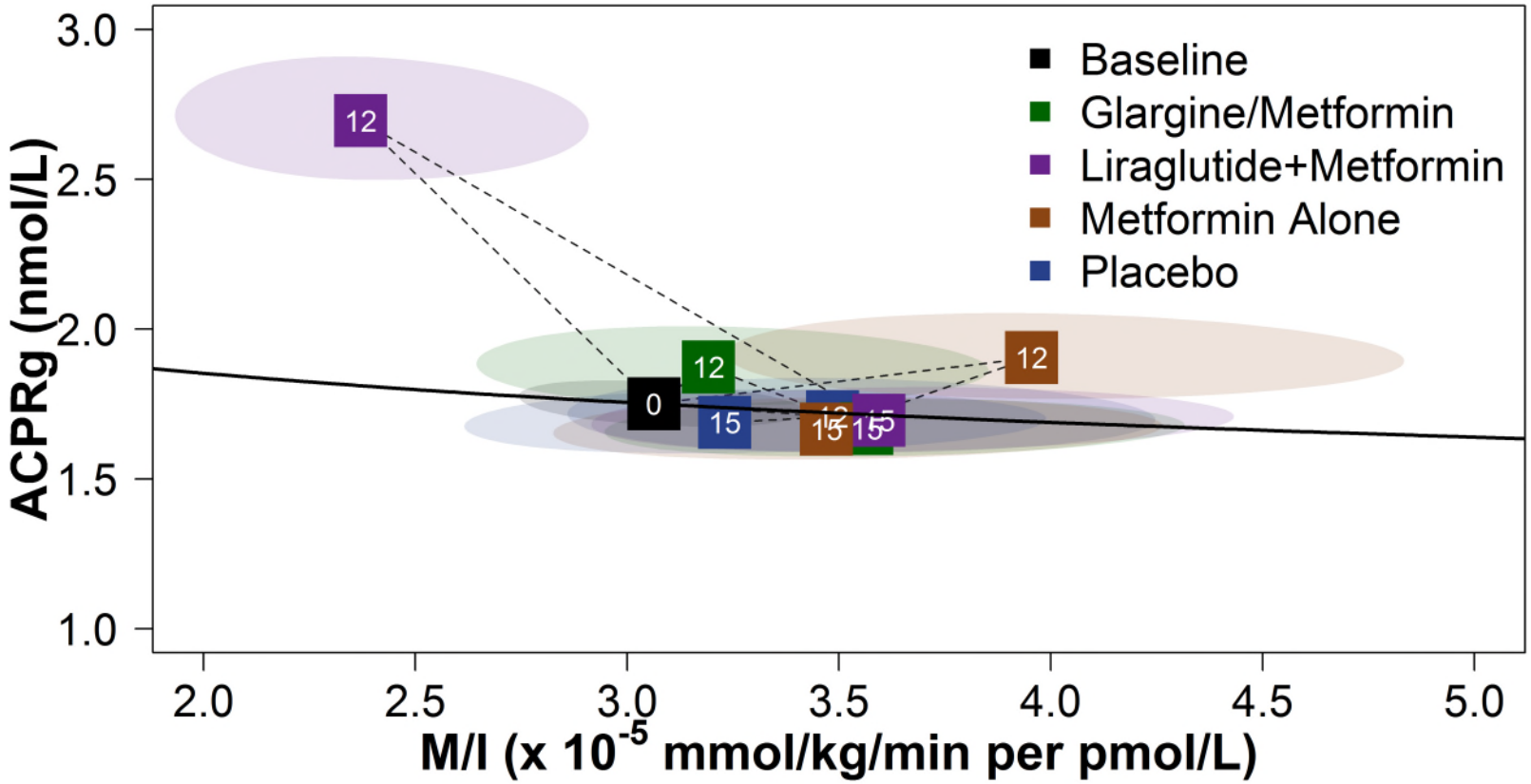

Kahn SE et al. Nature 2006;444:840.

# On-Treatment and Post-Treatment Effects on Relationship of Insulin Sensitivity and Insulin Release Differ Between Youth and Adults



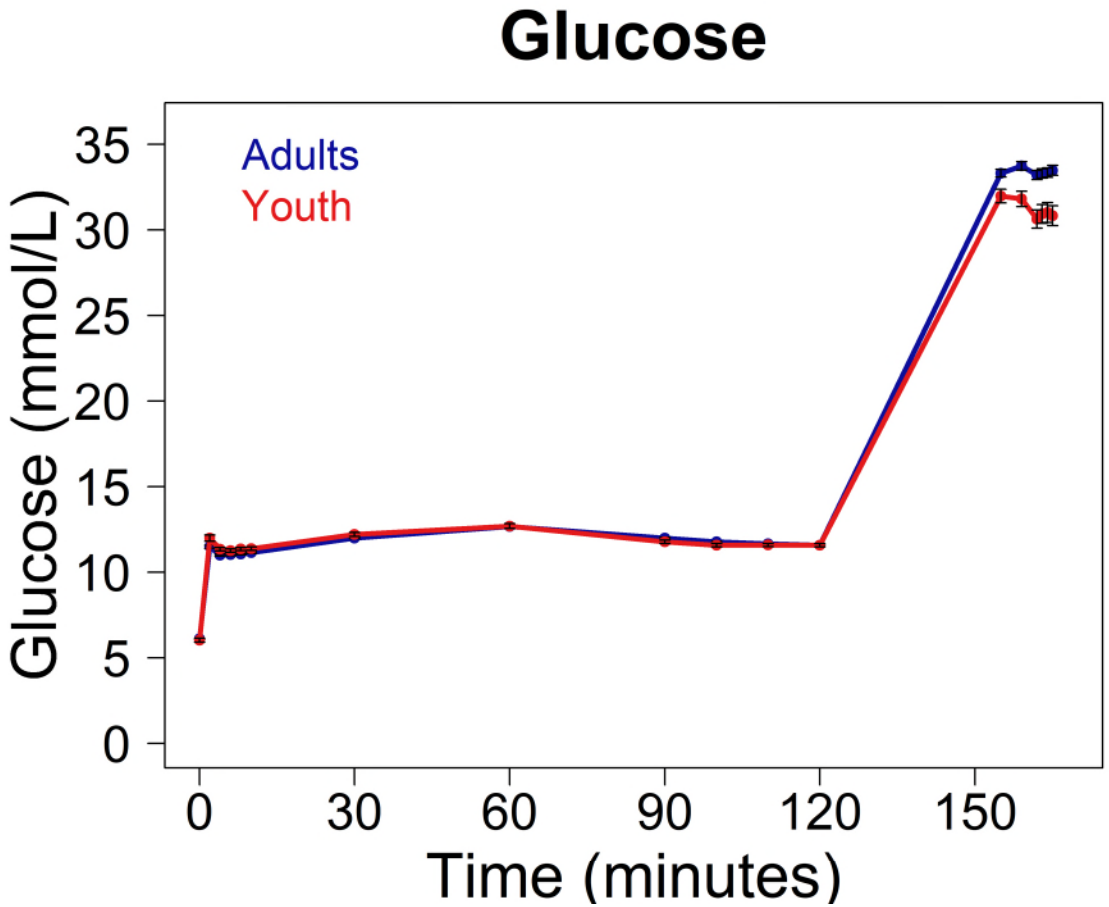

The RISE Consortium: Diabetes, 2019; 68:1670-1680

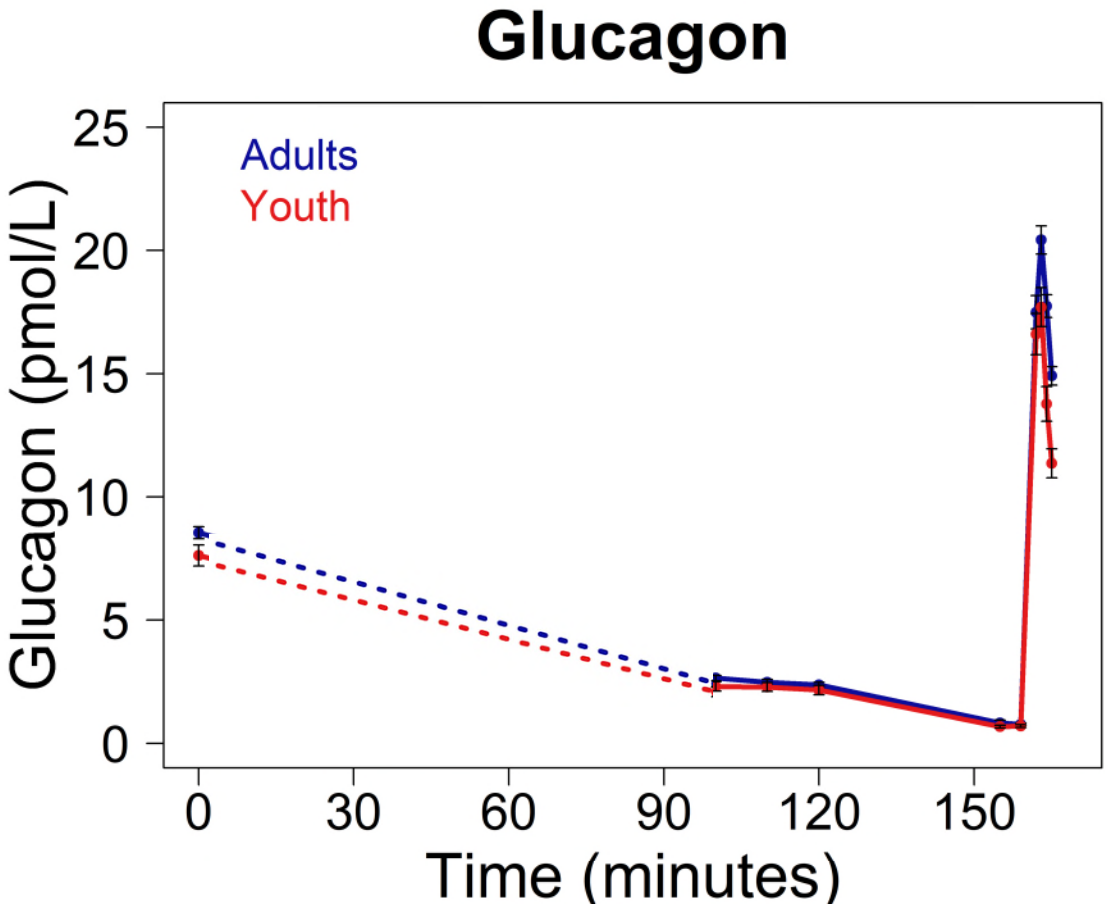
# On-Treatment and Post-Treatment Effects on Relationship of Insulin Sensitivity and Insulin Release in Adults



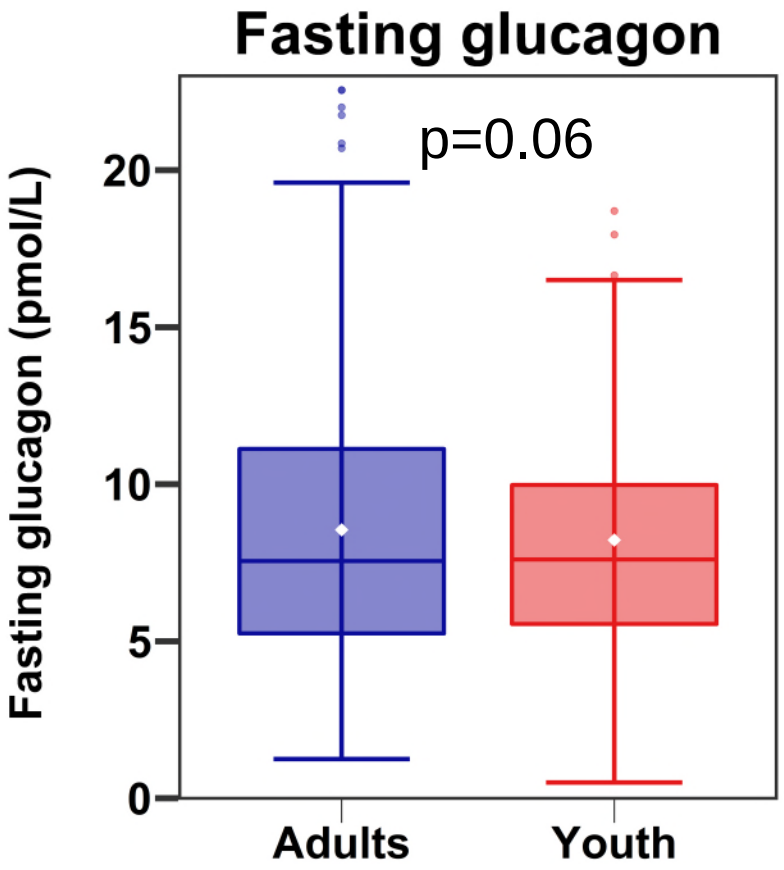

The RISE Consortium: Diabetes, 2019; 68:1670-1680

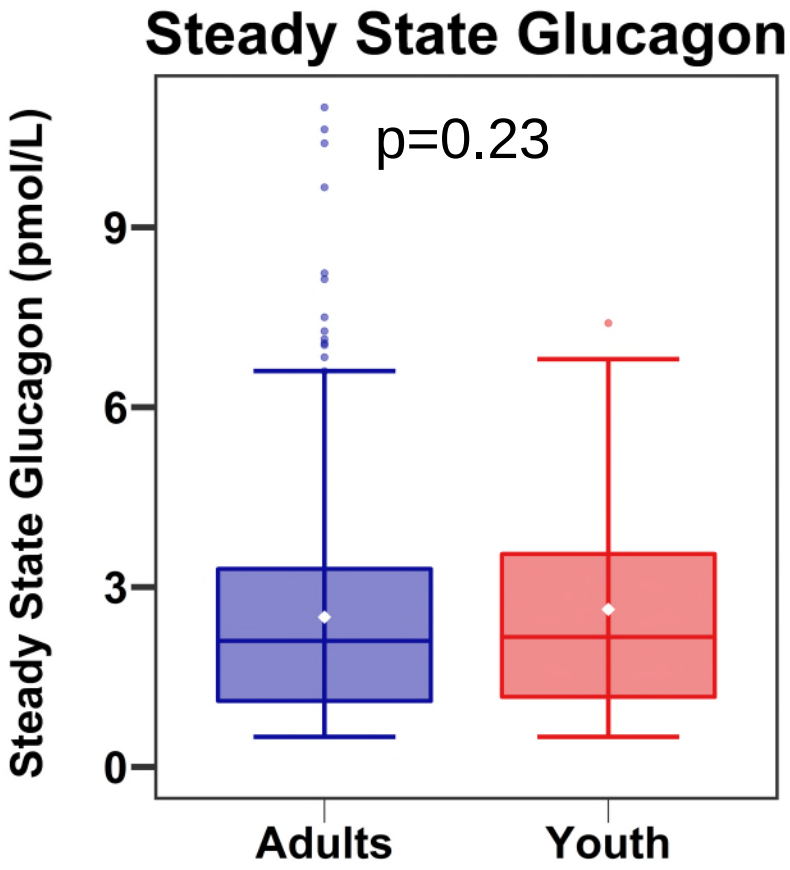
# Baseline Clamp Glucose and Glucagon Profiles in Youth vs. Adults

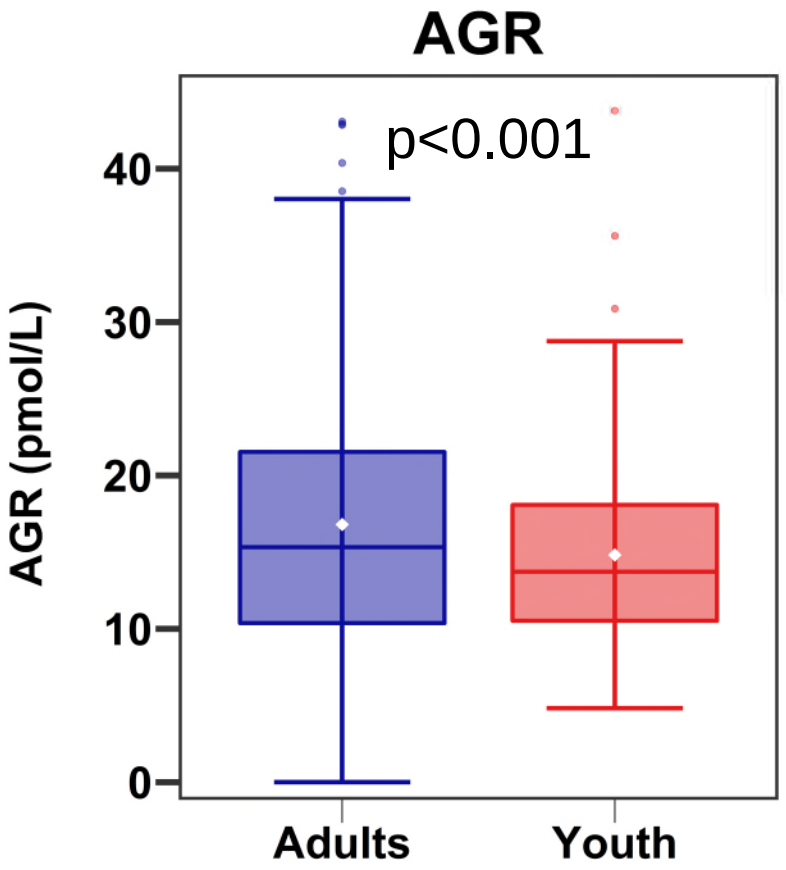


# Glucagon Concentrations during Clamp
## Youth vs. Adults



# Summary of Differences in Youth and Adults in RISE

- Youth with IGT and T2D are more insulin resistant and secrete more insulin than adults.
- β-cells in youth with IGT are more responsive to glucose than adults with IGT.
- β-cells in youth with T2D are not more responsive to glucose than adults with T2D.
- Insulin response for sensitivity in youth declines over time despite 12 months treatment with metformin or glargine followed by metformin, while adult treatment arms are stable.
- Adults show modest benefit in β-cell function while on liraglutide plus metformin treatment.

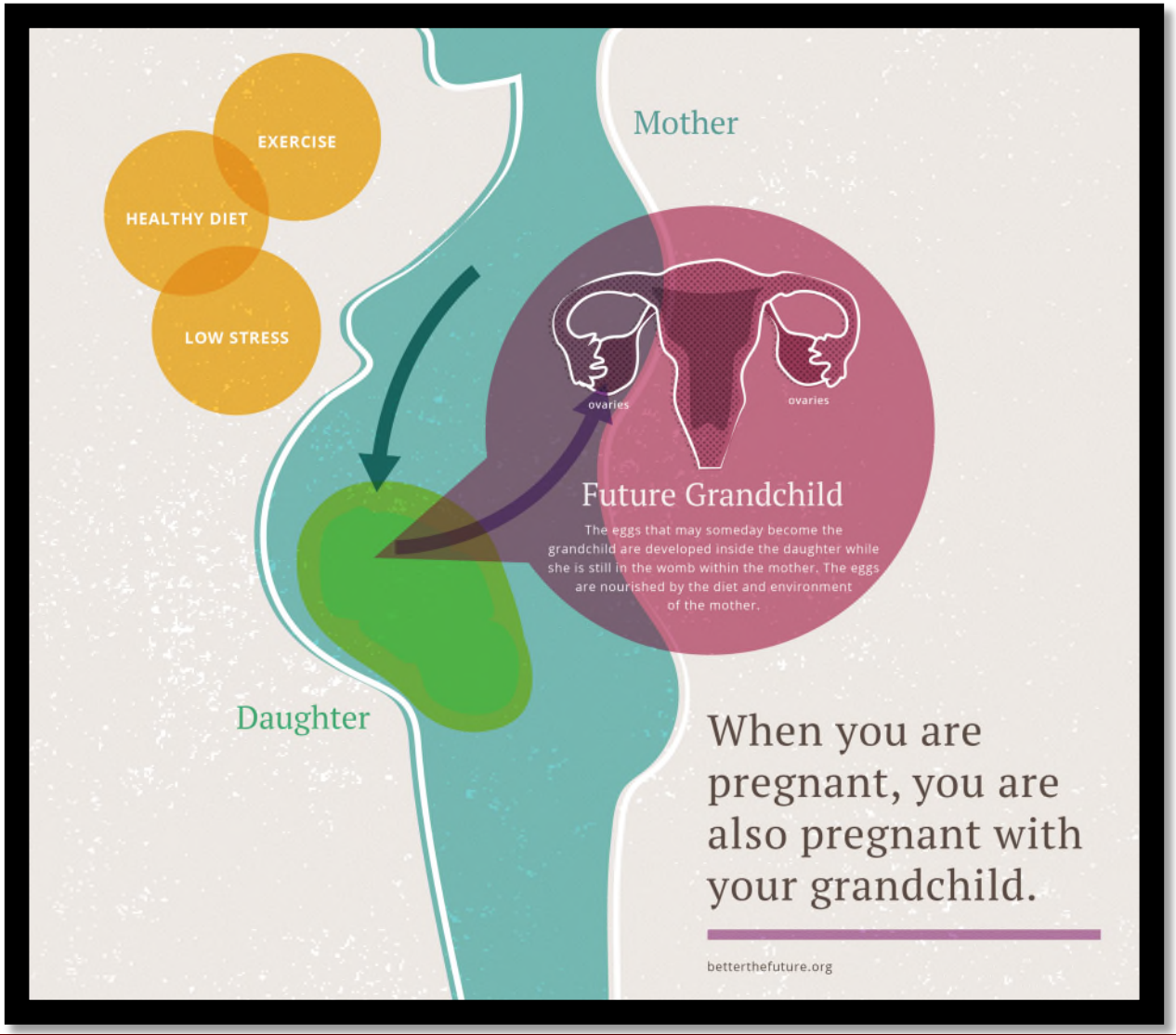
# Conclusions from RISE

In RISE, interventions to

- reduce insulin resistance (metformin)
- reverse glucose toxicity (glargine before metformin)
- stimulate insulin secretion (liraglutide) or

failed to induce *durable* improvements in β-cell function over 12 months (medications) or 24 months (surgery).

# Genetic Factors Impact Risk for Youth-Onset T2D




betterthefuture.org

# Progress in Diabetes Genetics in Youth (ProDiGY) and Accelerating Medicines Partnership (AMP) T2D GENES Studies

| ProDiGY WES | Healthy Adult Controls WES |
|---|---|
| Quality control measures | |
| Ancestry matching of cases/controls | |
| 3,005 matched cases and 9,777 controls | |
| Single variant association | |
| Gene-level burden | |

Kwak SH, The ProDiGY Consortium: Nature Metabolism. Vol 6:226, 2024

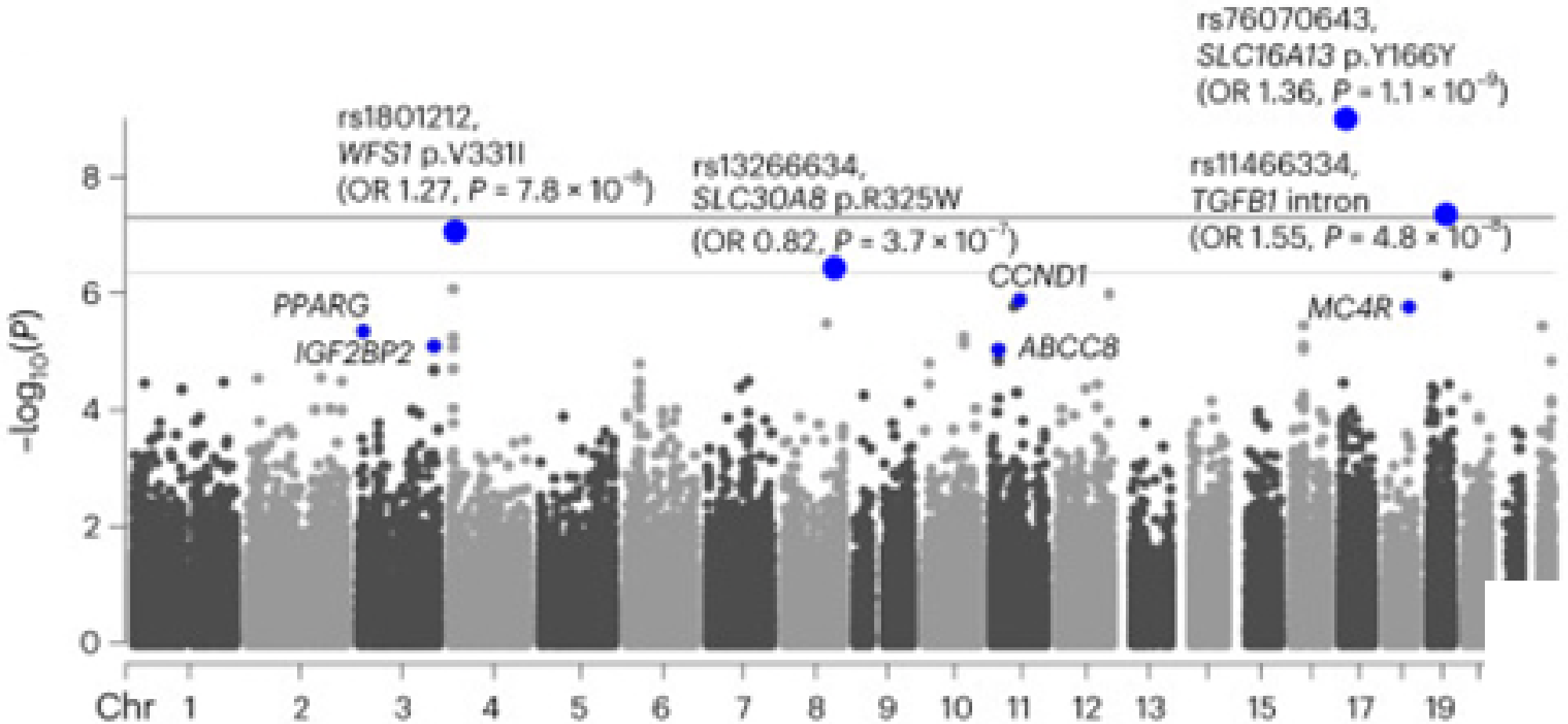
# Progress in Diabetes Genetics in Youth (ProDiGY) and Accelerating Medicines Partnership (AMP) T2D GENES Studies

***WFS1*** – ER transmembrane glycoprotein

***SLC30A8*** – ZNT8

***SLC16A13*** – MCT13

***TGFβ1*** – cell growth/diff

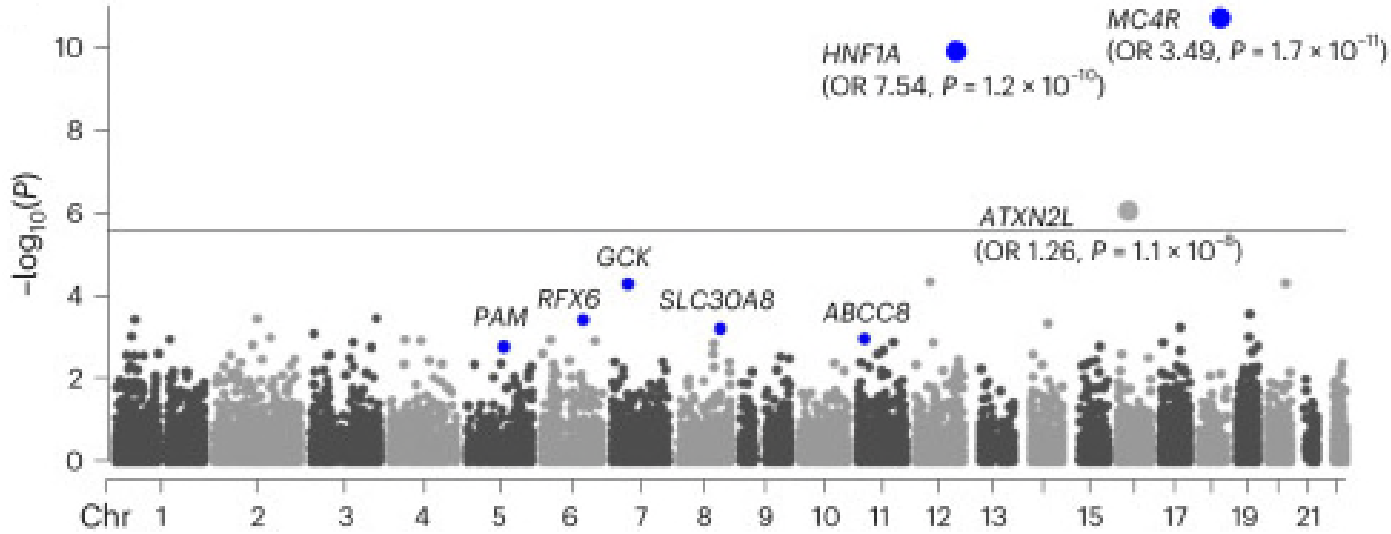



Kwak SH, The ProDiGY Consortium: Nature Metabolism. Vol 6:226, 2024

## Progress in Diabetes Genetics in Youth (ProDiGY) and Accelerating Medicines Partnership (AMP) T2D GENES Studies

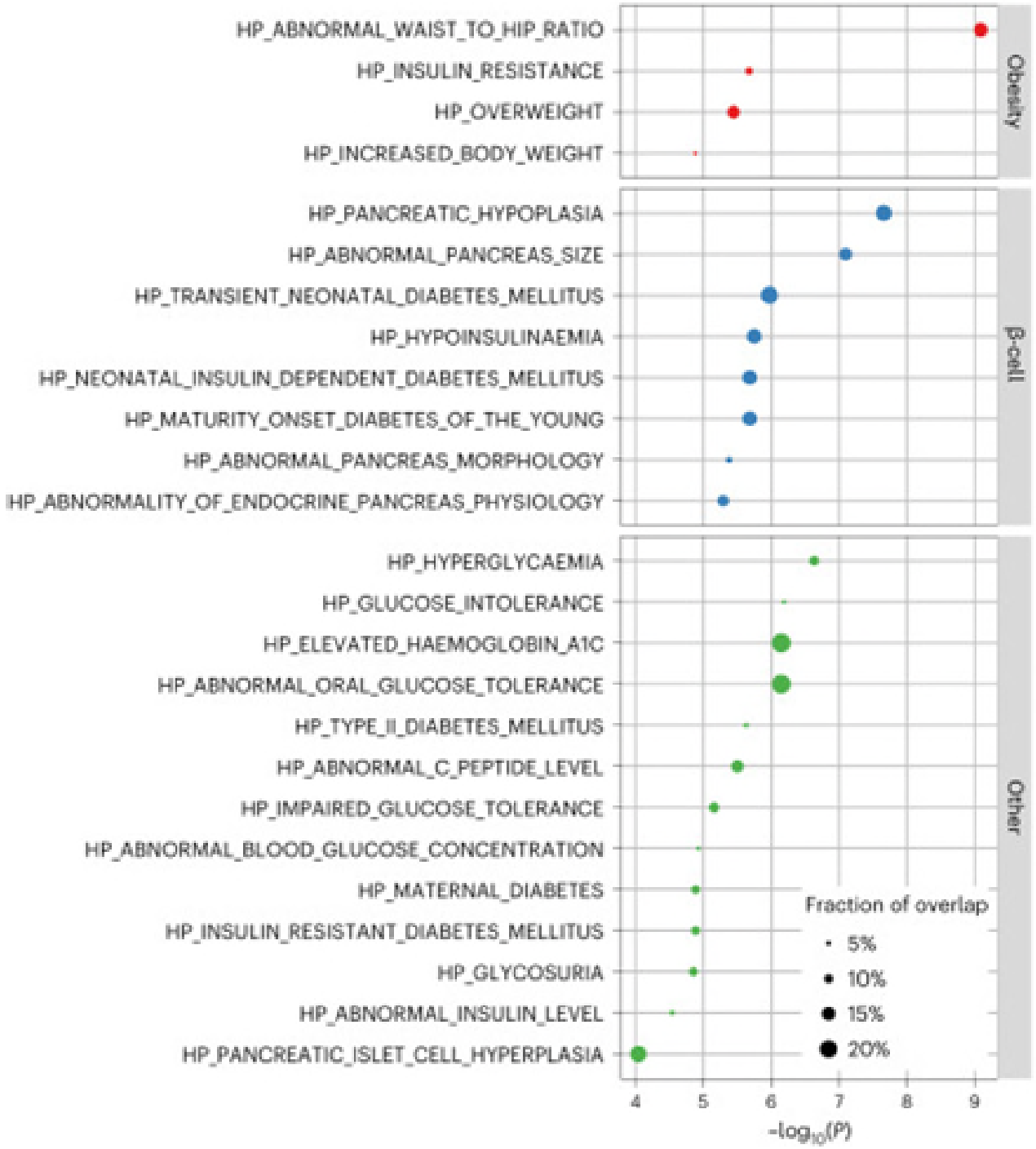
- Three genes with exome-wide significant associations with youth-onset T2D

- All rare
  - ***MC4R*** (OR 3.5)
  - ***HNF1A*** (OR 7.54)
  - ATXN2L (OR 1.26) – strong linkage disequilibrium with intronic variant of SH2B1 (BMI variability)




- Strongest adult T2D genetic risk factors also present in youth T2D *at greater frequency*

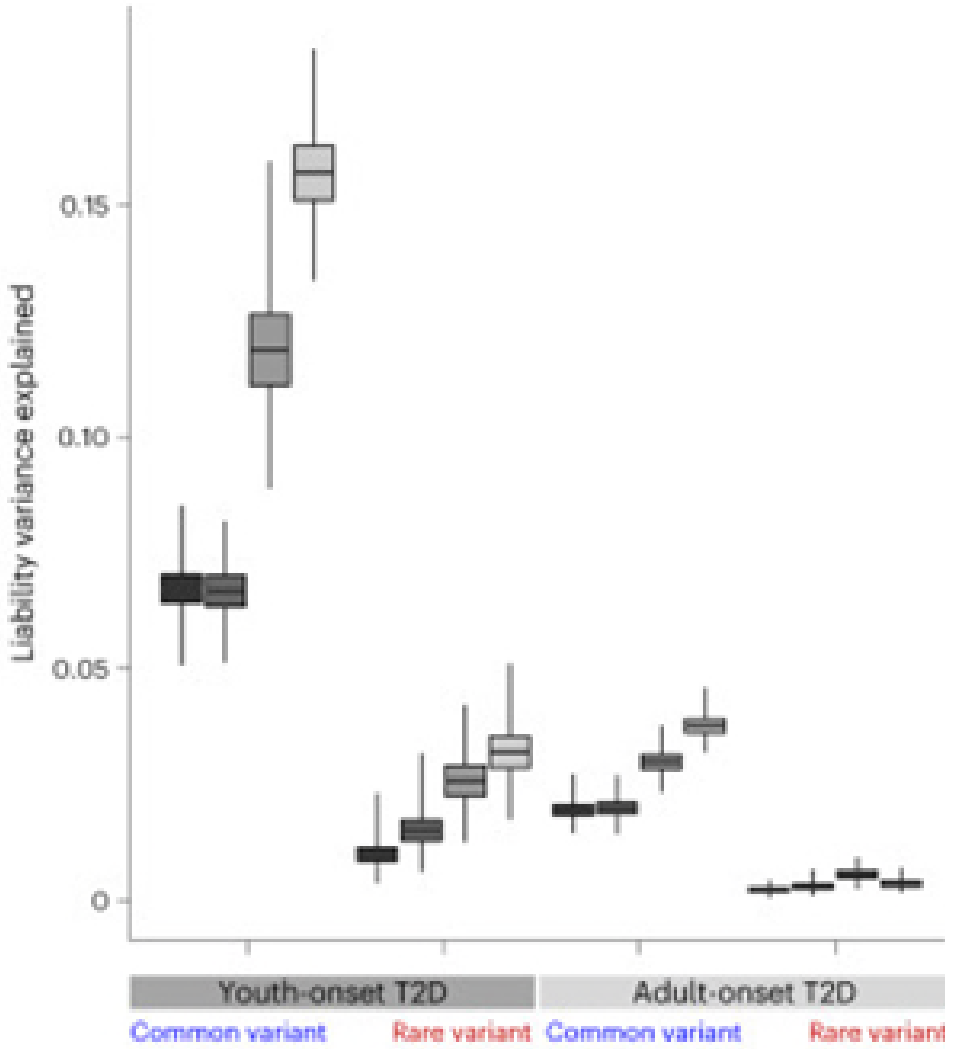
Kwak SH, The ProDiGY Consortium: Nature Metabolism. Vol 6:226, 2024




# Genotype – Phenotype Associations

- Central adiposity
- Pancreatic hypoplasia
- Glucose measures

Kwak SH, The ProDiGY Consortium: Nature Metabolism. Vol 6:226, 2024

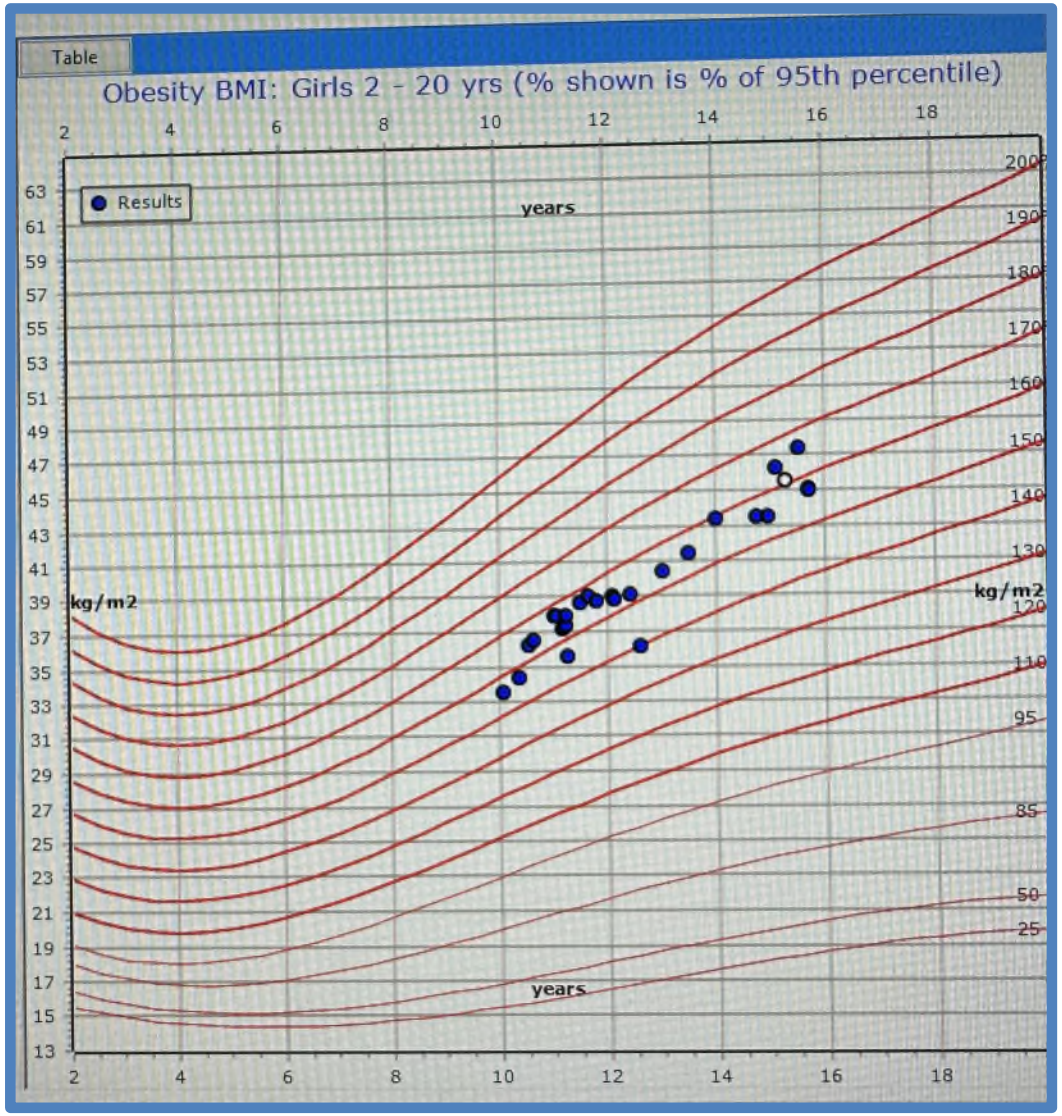

Liability variance explained
0.15
0.10
0.05
0
Youth-onset T2D
Adult-onset T2D
Common variant
Rare variant
Common variant
Rare variant

# Summary - Genetic Factors and Youth-Onset T2D

- Youth-onset T2D is associated with more rare and common genetic variants than adult-onset T2D:
  - Common genetic variants (~13%)
  - Rare genetic variants (~3-4%)
  - Monogenic variants (<3%)
  - Combined variants (<3%)
- Genetic risk factors have a greater associations with central adiposity, pancreatic factors, and hyperglycemia in youth-onset T2D than adult T2D.
- Clinical heterogeneity of youth-onset T2D is influenced by the frequency of contributing genetic risk factors.

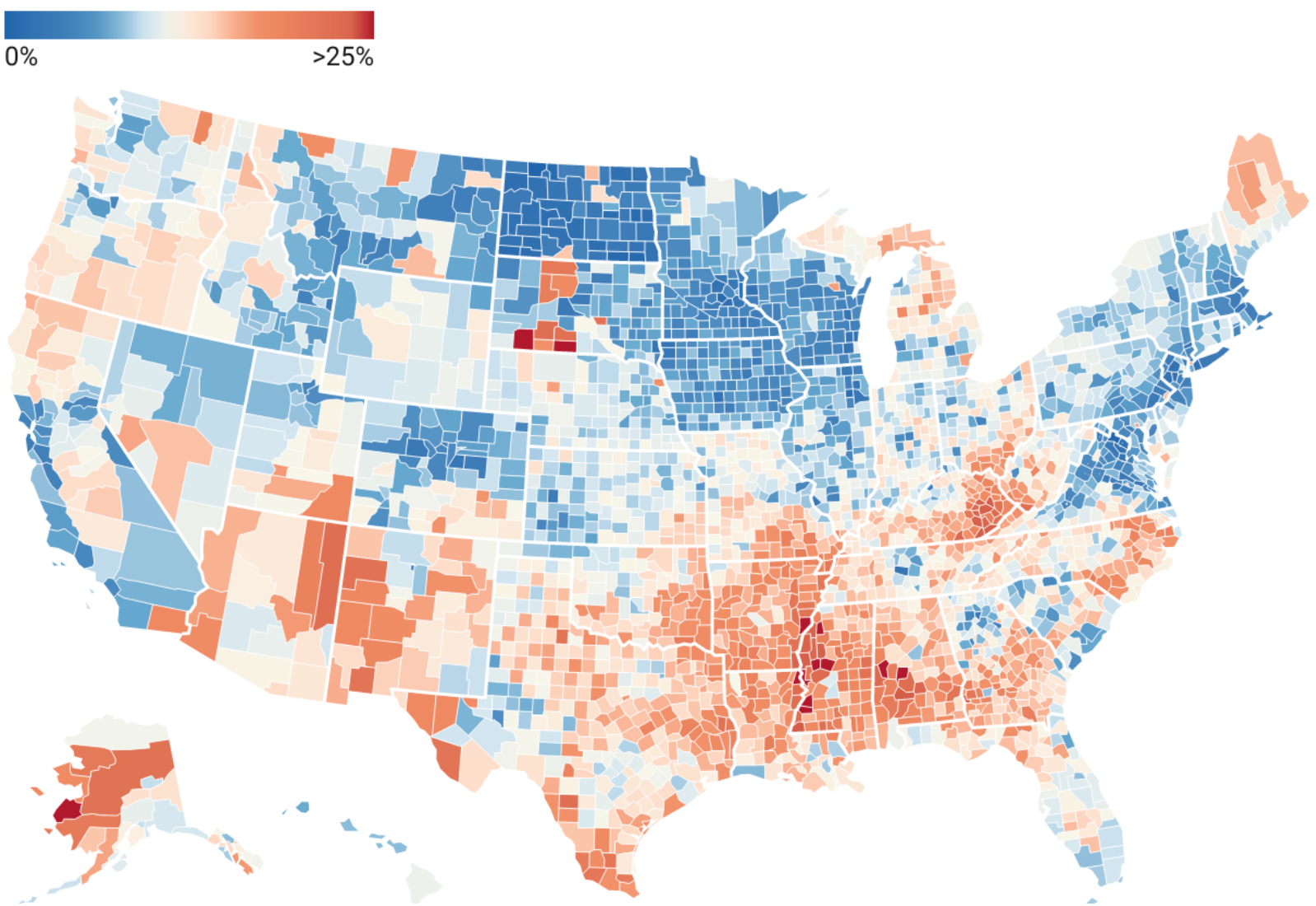
# Case History – 14 yo

- Caring for siblings while mom works; food insecure
- Physical Exam
  - BP 136/87
  - BMI 45 kg/m$^2$ (>140% of the 95$^{th}$ percentile)
  - Extensive acanthosis nigricans
- Lab Studies
  - HbA1c 7.0%; FPG 102 mg/dL
  - Fasting lipids: cholesterol 210 mg/dL
  - Low HDL, elevated LDL; TG 357 mg/dL



# Food Insecurity in America

USDA, 2018



# Maslow's Hierarchy of Needs

# Satter's Hierarchy of Food Needs

Instrumental Food

Novel Food

Good-Tasting Food

Reliable Access to Food

Acceptable Food

Enough Food

Satter. Soc Nutr Ed Behav 2007

# Multiple biological mechanisms work in concert to defend weight

# Adverse Childhood Events and Modern Diets Impact β-cell Stress

↑ *de novo* lipogenesis

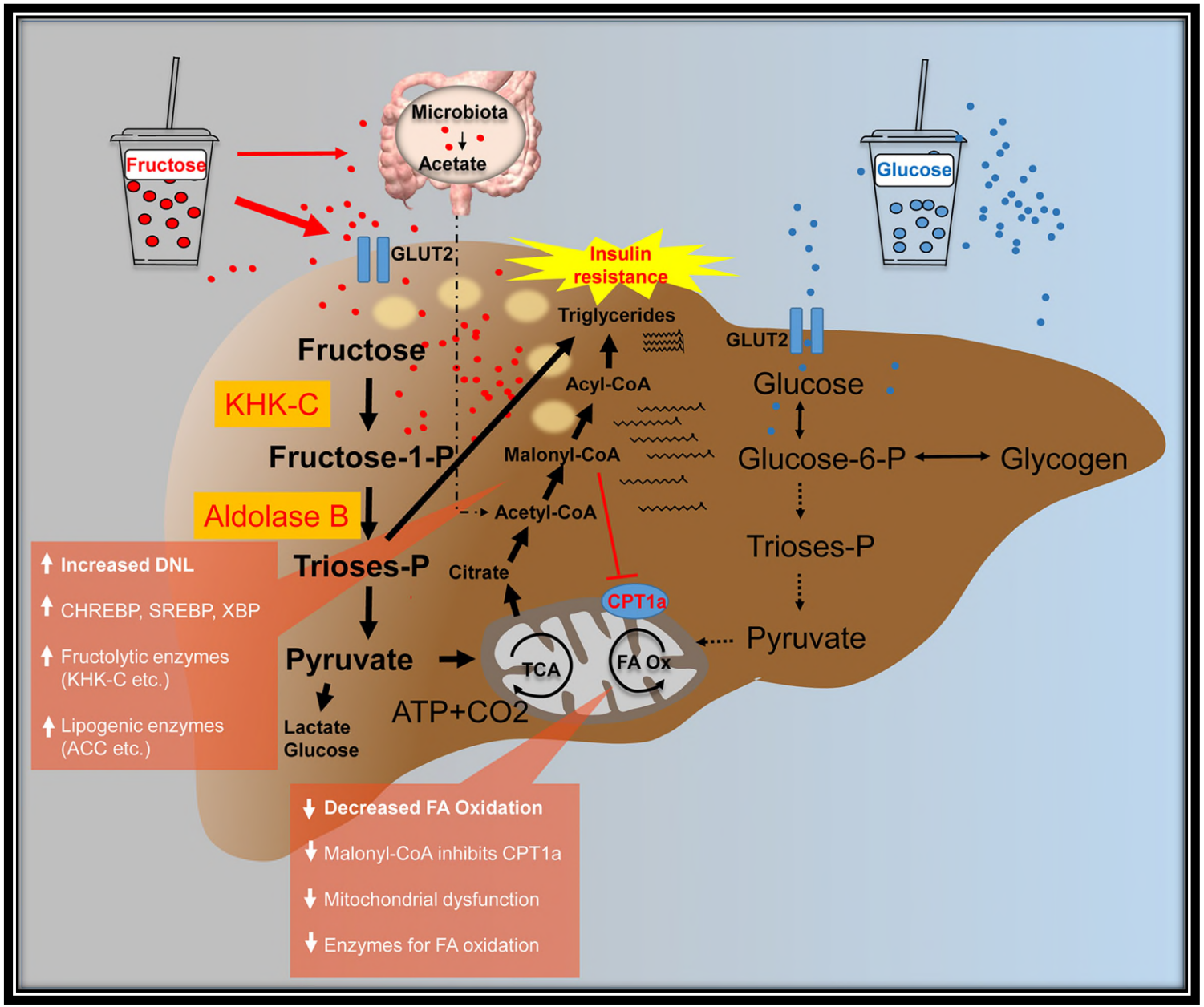
↑ ectopic fat

↑ inflammation

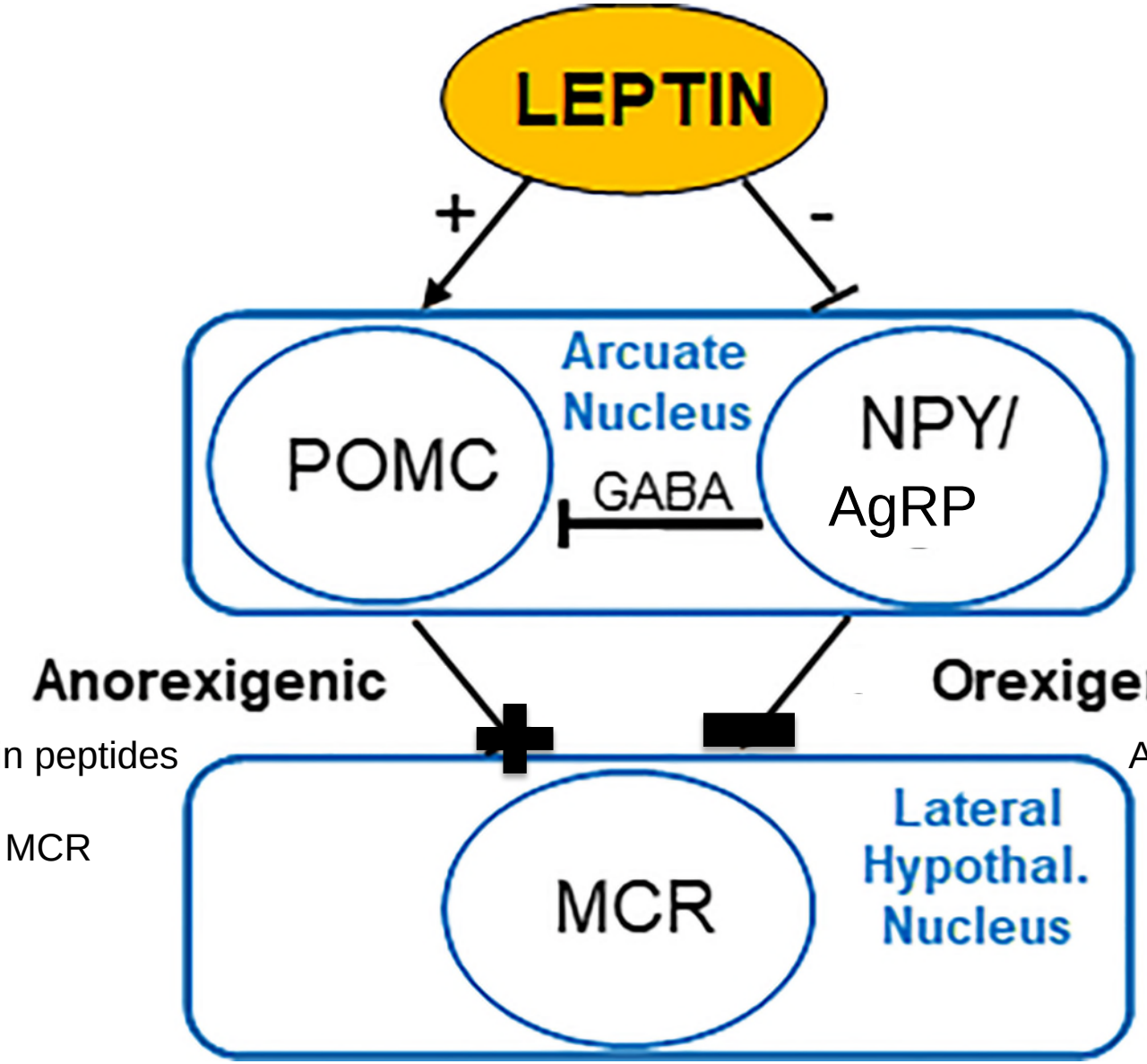
↑ circulating triglycerides

↓ hepatic insulin sensitivity

↓ whole-body insulin sensitivity



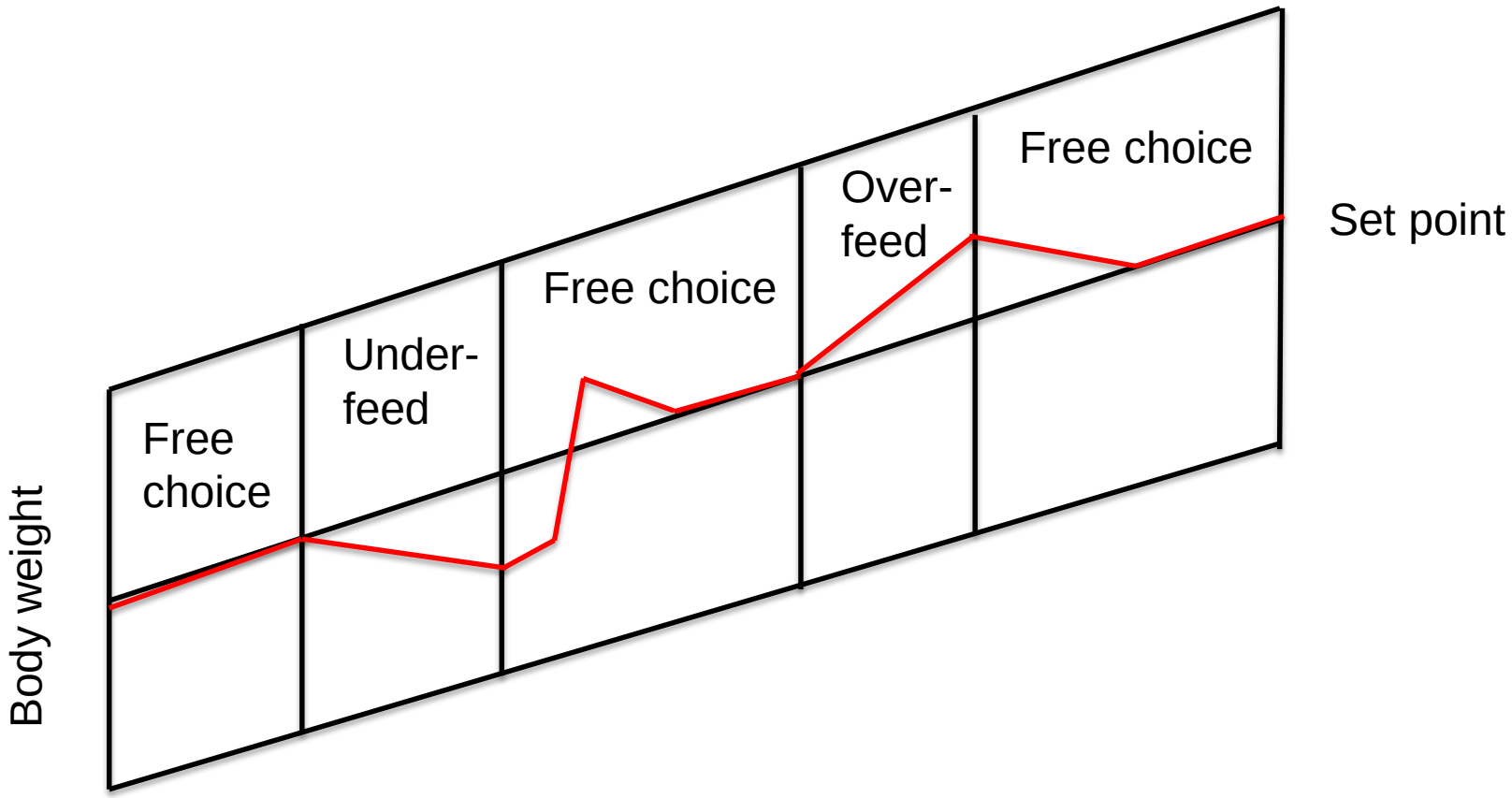

Geidl-Flueck and Gerber. Journal of Endocrinology 2023; 257.



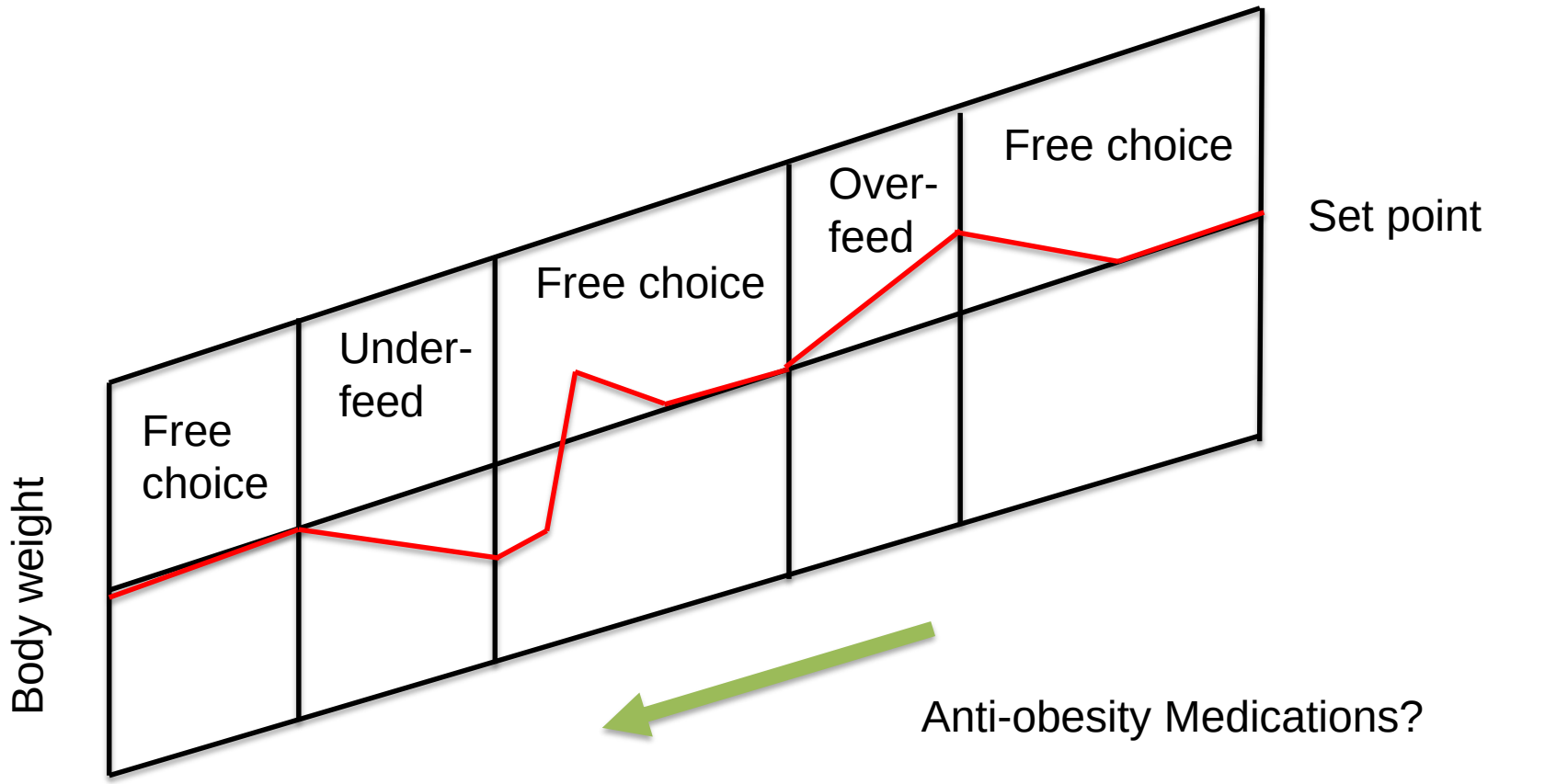

Melanocortin peptides
MSH
Agonists to MCR

Antagonists to MCR

# Set-Point Theory



# Set-Point Reduction?



# Case History – 15 yo

- Not feeling well – headaches, tired all the time, has had a skin infection that is getting worse
- Family is struggling; School is hard

- Physical Exam
  - BP 130/78
  - BMI has decreased a bit

- Lab Studies
  - HbA1c 11.0%;  random PG 582 mg/dL
  - Urine ketones moderate

# Insulin Resistance + Insulin Insufficiency

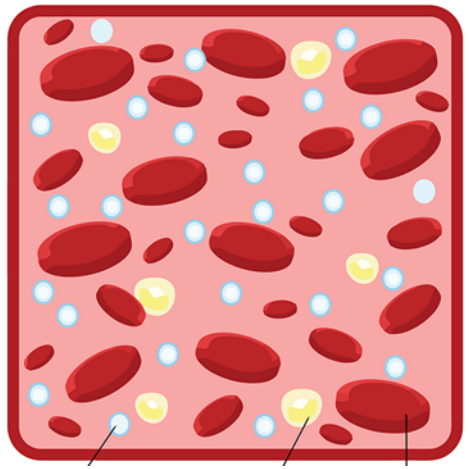
**Glucagon - Catabolic**

↑ Glycogenolysis

↑ Gluconeogenesis

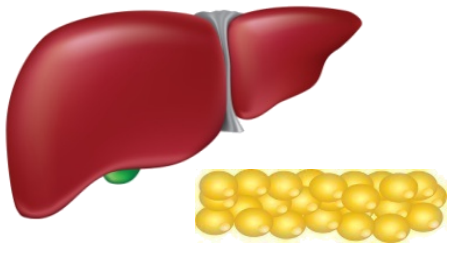
↑ BLOOD GLUCOSE

HYPERGLYCEMIA

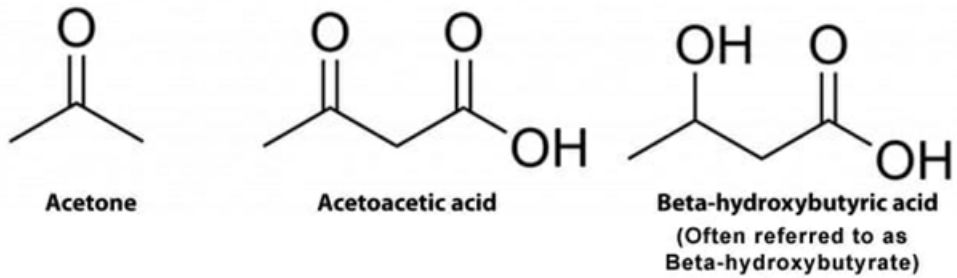


***NOT ENOUGH INSULIN***

***↓↓↓ INSULIN ACTION***



+ Ketosis




**Insulin - Anabolic**

↑ Glucose transport

↑ Glycogen stores

↓ Gluconeogenesis

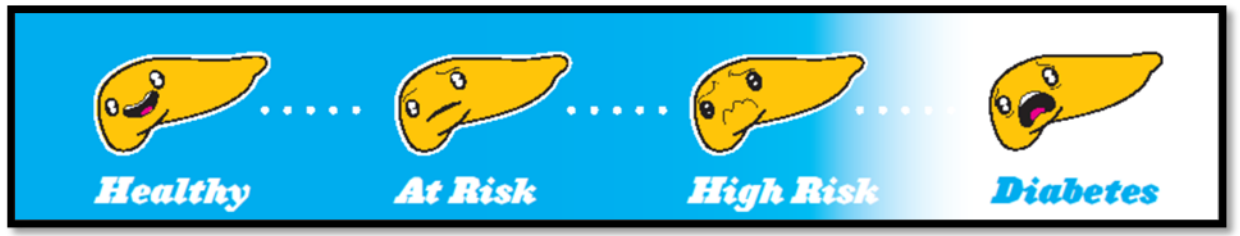
↓ BLOOD GLUCOSE

# Precision Medicine Approach – We Have Work to Do!

***Prevent and treat obesity***

***Consider genotype/phenotype correlations***

***Reduce stress on the pancreas and liver***




***Therapies that reduce insulin resistance***

***Maintain β-cell fx – elusive to date***

***Treat diabetes expediently***

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