



World Congress Insulin Resistance  
**DIABETES & CARDIOVASCULAR DISEASE**  
**LIVEIN-PERSONONLINE**

A Tribute to Gerald  
Reaven  
1 December 2022



# Insulin Resistance, Insulin Secretion, Insulin Clearance: Who is the Culprit?

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# Dualities of Interest

Advisory Board, Consulting and Lectures

Anji Pharmaceuticals

Merck

Bayer

Novo Nordisk

Boehringer Ingelheim

Pfizer

Casma Therapeutics

Third Rock Ventures

Eli Lilly

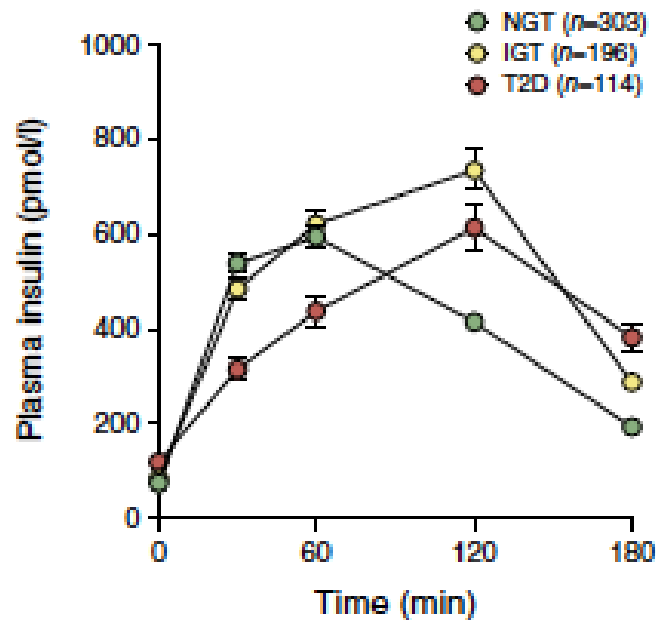
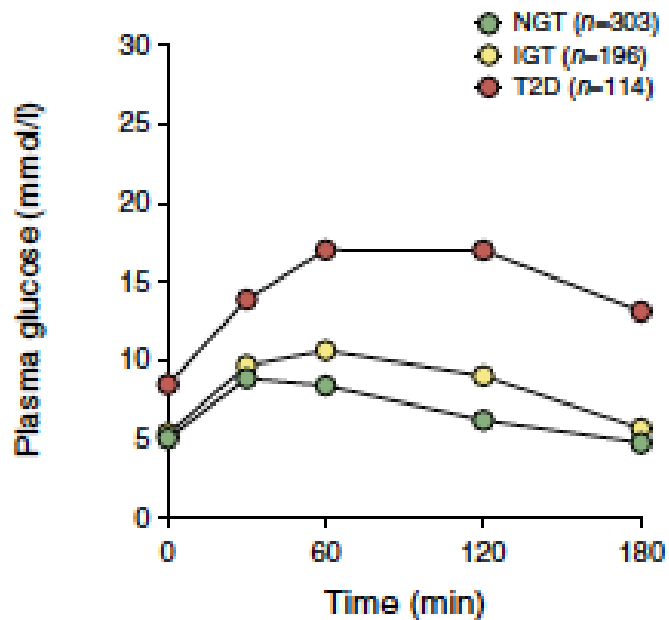
# Outline

1. Glucose tolerance, insulin resistance and insulin secretion
  1. Cross-sectional studies
  2. Longitudinal studies
2. Insulin clearance
3. Filling the knowledge gaps

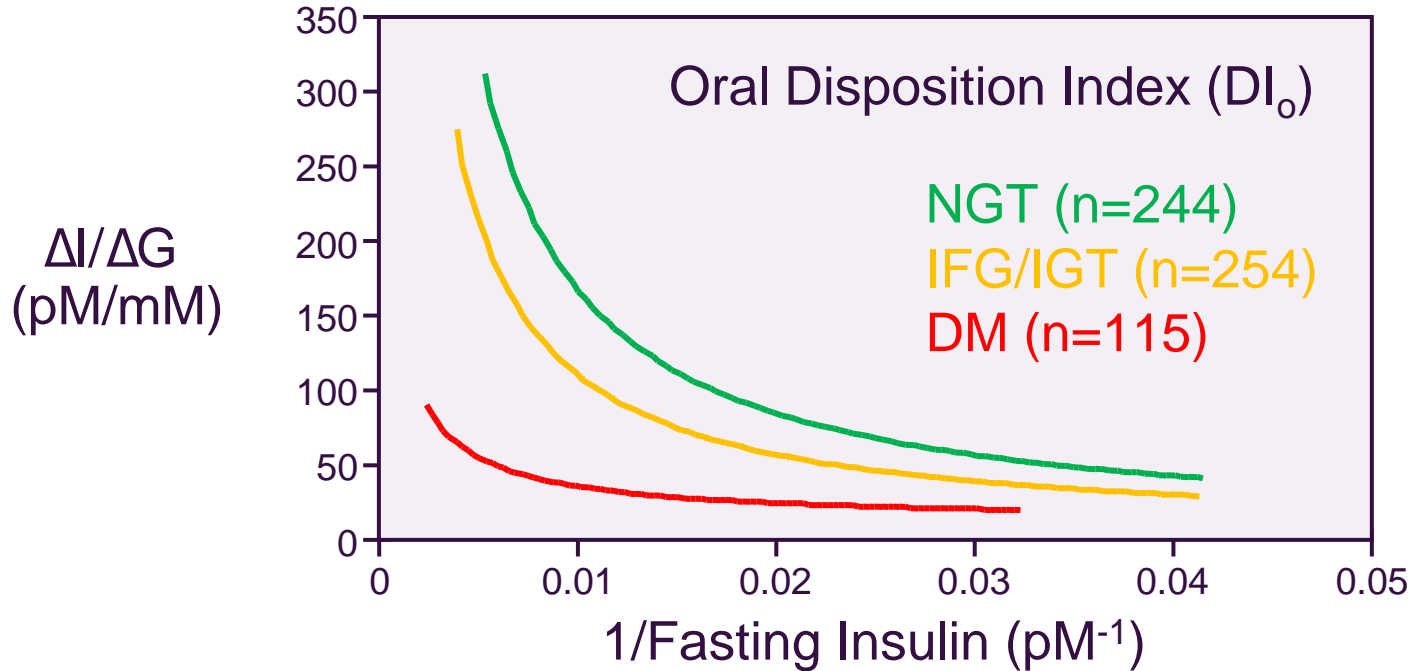
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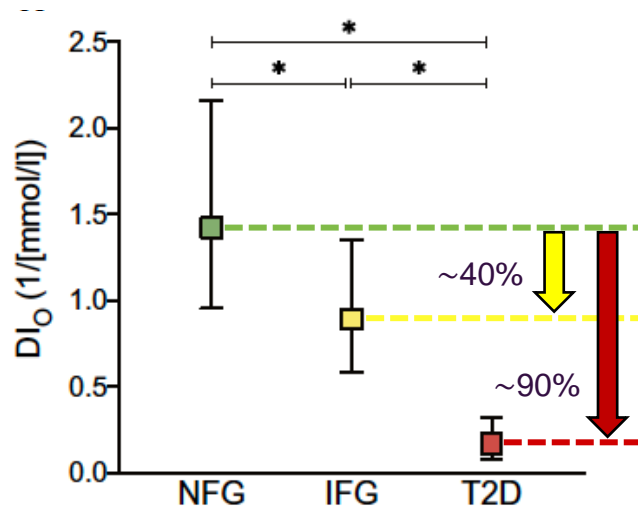
# OGTT Glucose and Insulin Profiles in Individuals with Different Glucose Tolerance



# The OGTT Hyperbolic Relationship is Shifted with Decreasing Glucose Tolerance

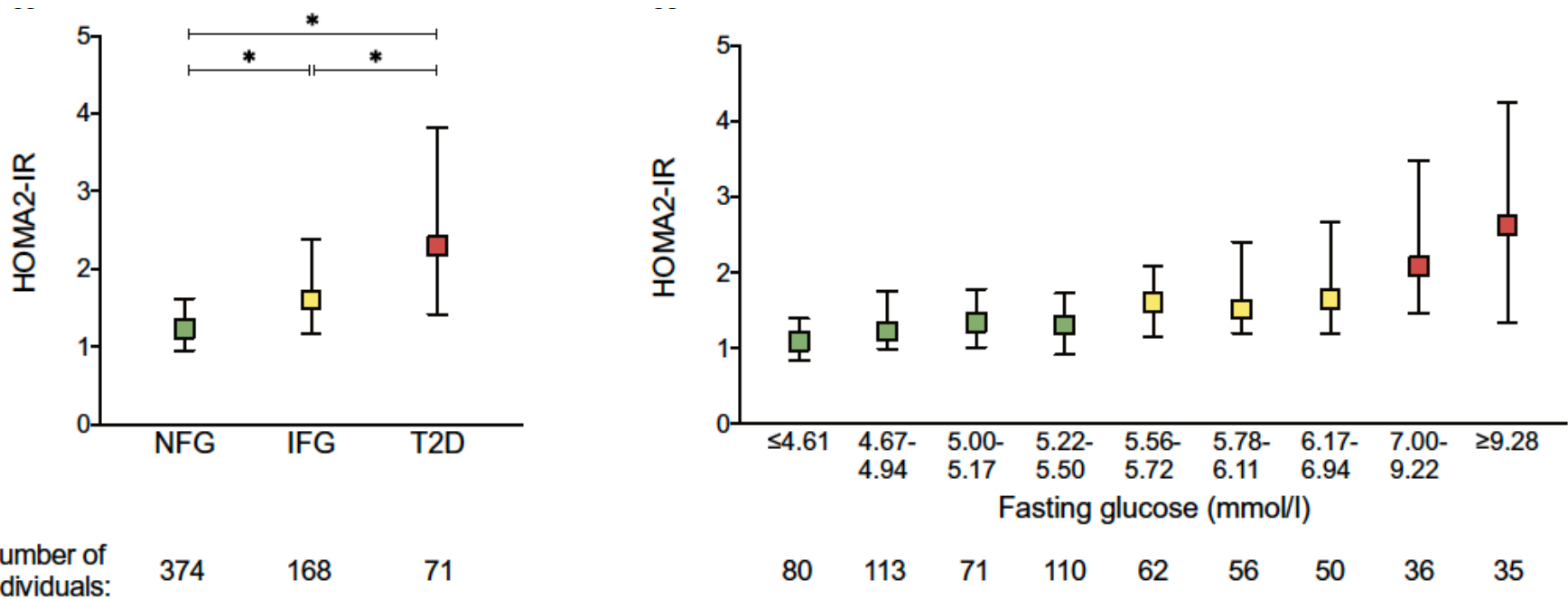


# Relationship of Glucose Tolerance and Fasting Glucose with $\beta$ -cell Function



Number of individuals: 374 168 71

# Relationship of Glucose Tolerance and Fasting Glucose with Insulin Resistance

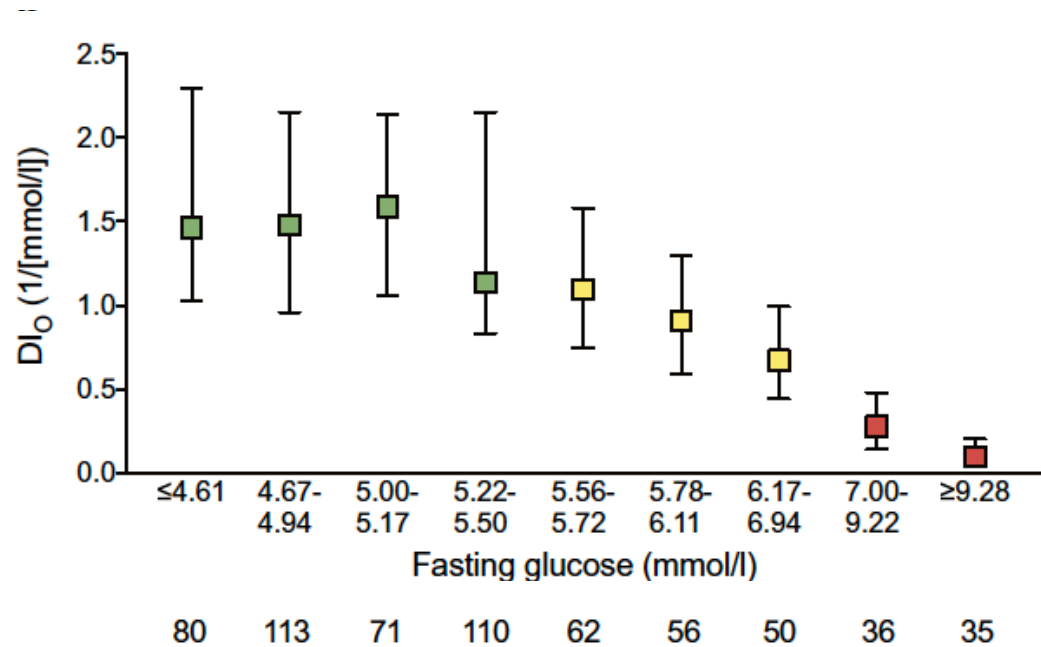




# Relationship of Glucose Tolerance and Fasting Glucose with Beta-cell Function

African Americans  
Japanese Americans  
Latin Americans  
White Americans

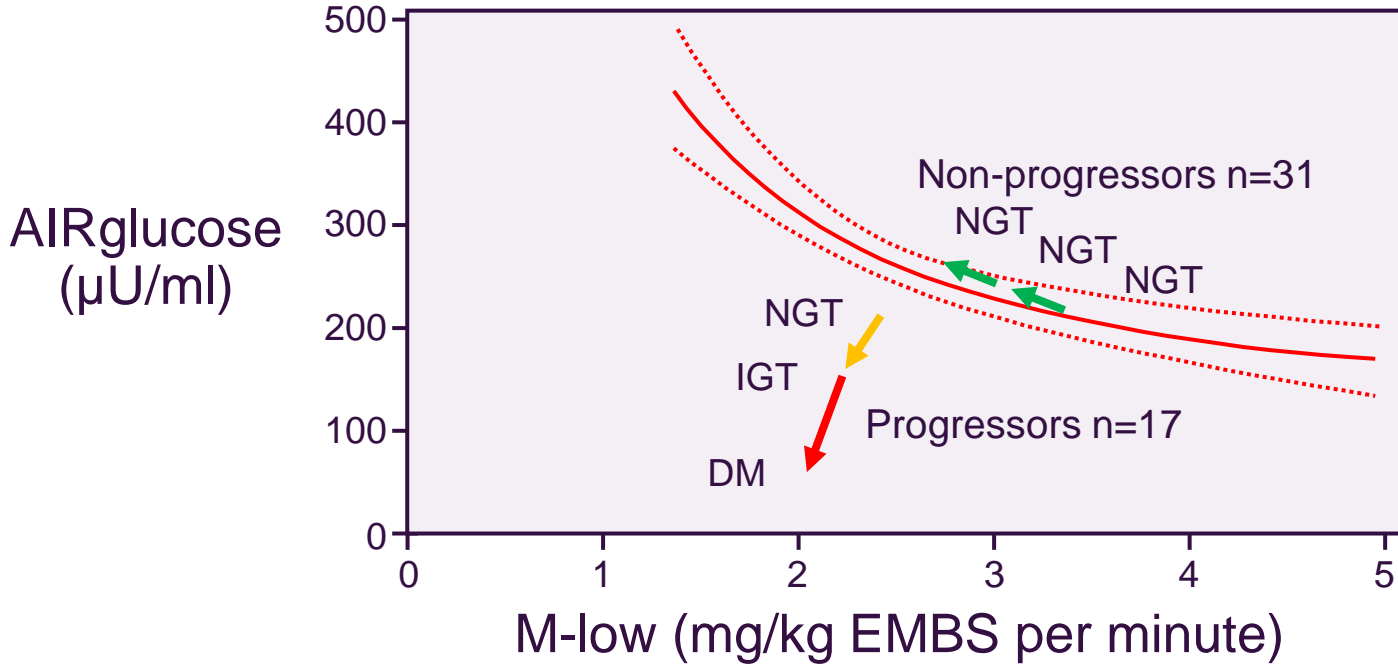
Esser N, Kahn SE: unpublished observation



# Outline

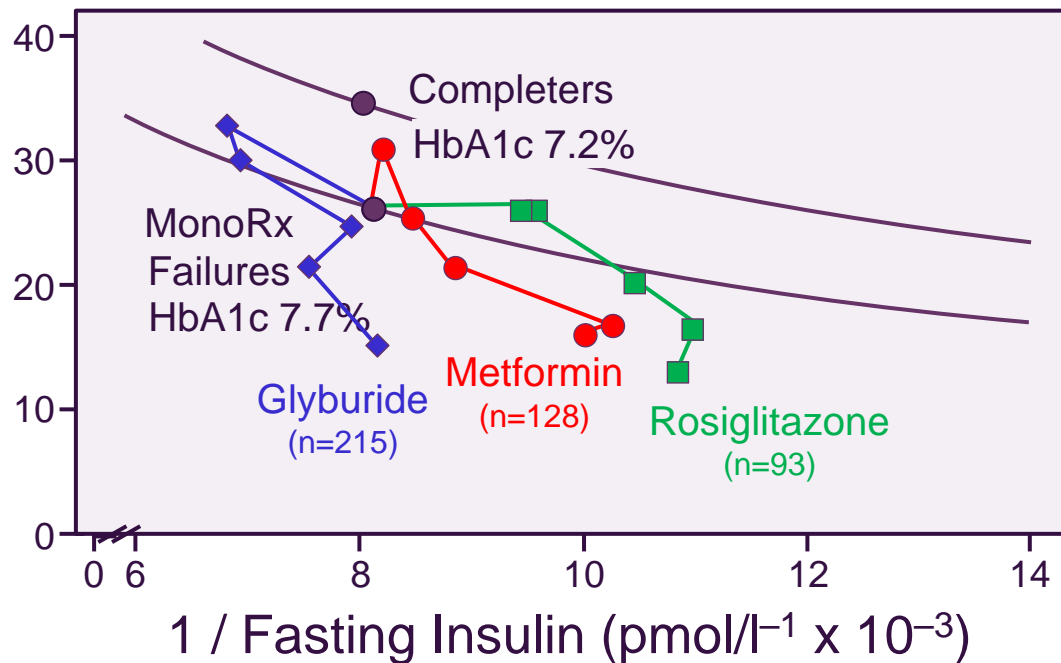
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# Progressive Loss of $\beta$ -cell Function in Pima Indians

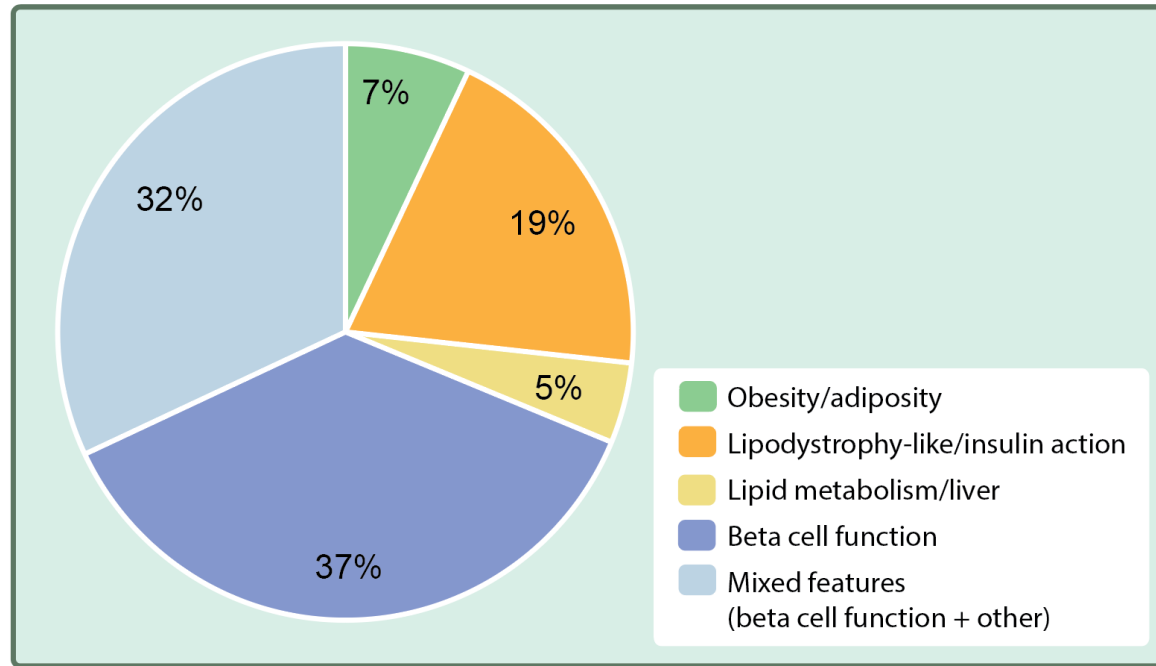


# Change in $\beta$ -cell Function Over Time in Monotherapy Failures with Type 2 Diabetes

Insulinogenic Index  
(pmol/mmol)



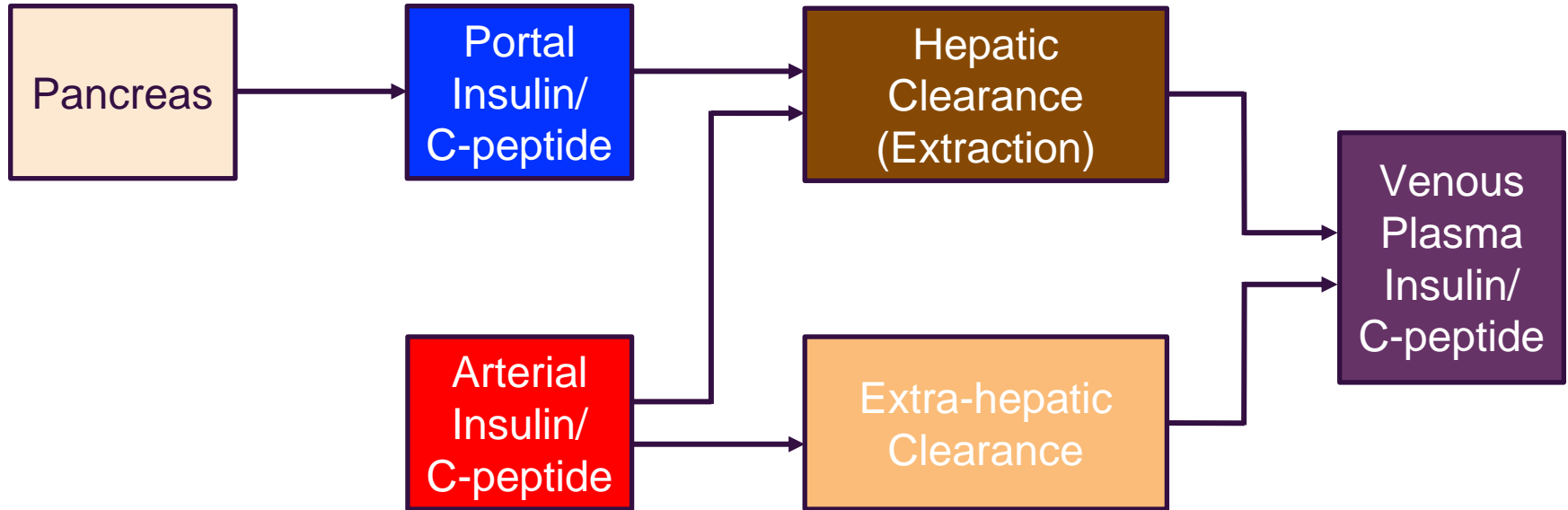
# Phenotypes Associated with 128 Gene Variants Linked to Type 2 Diabetes



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# Important Considerations in Estimating Insulin Clearance



# Definitions of Extraction and Clearance

## Extraction

Fraction eliminated upon each (single) passage through the liver

$\text{mol/L} \div \text{mol/L} = \text{fraction}$   
(expressed as a %)



# Definitions of Extraction and Clearance

## Clearance

The volume of fluid (e.g., blood, plasma) that flows through organs of elimination that is completely removed of the peptide/drug per unit of time

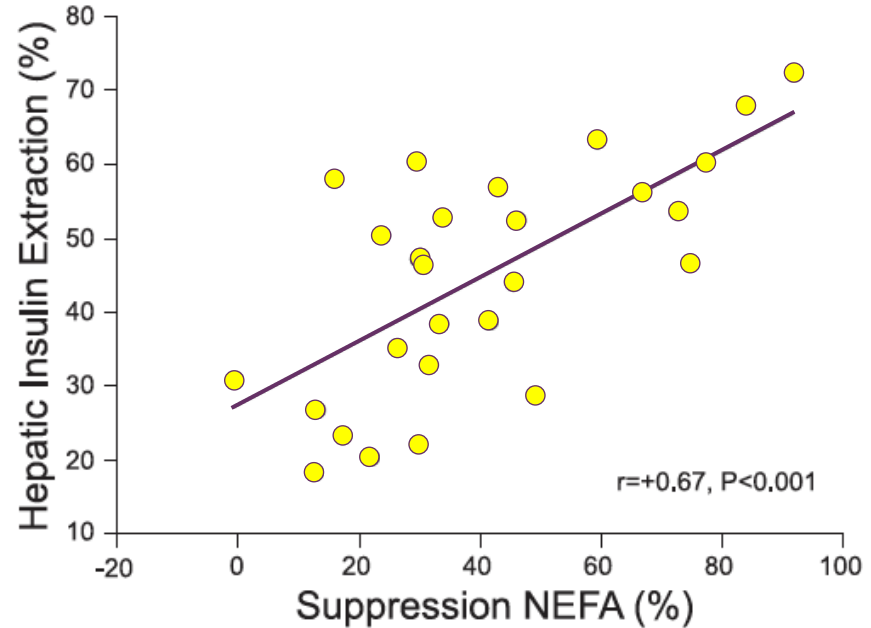
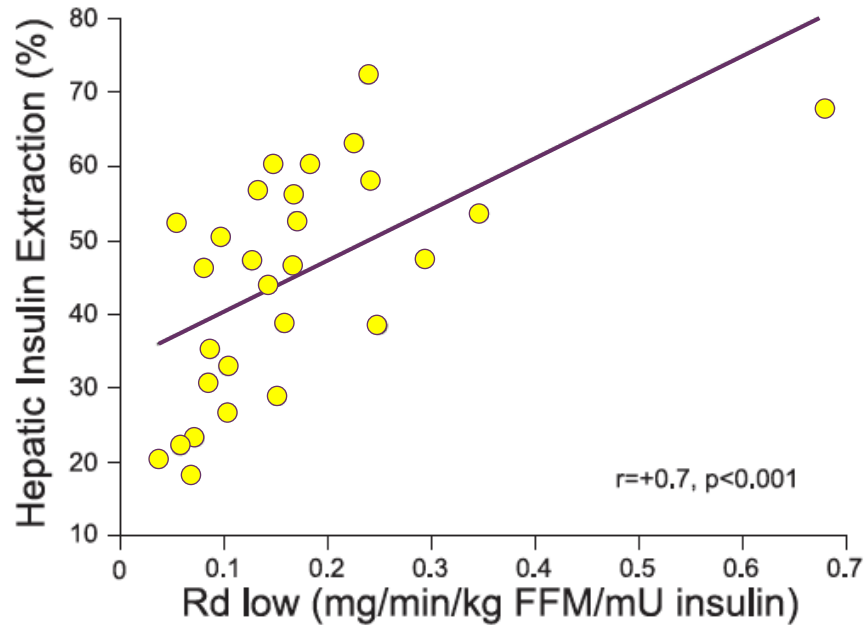
$$\text{mol} \div \text{mol/L} = \text{L}$$

(expressed per time unit, e.g. L/min)

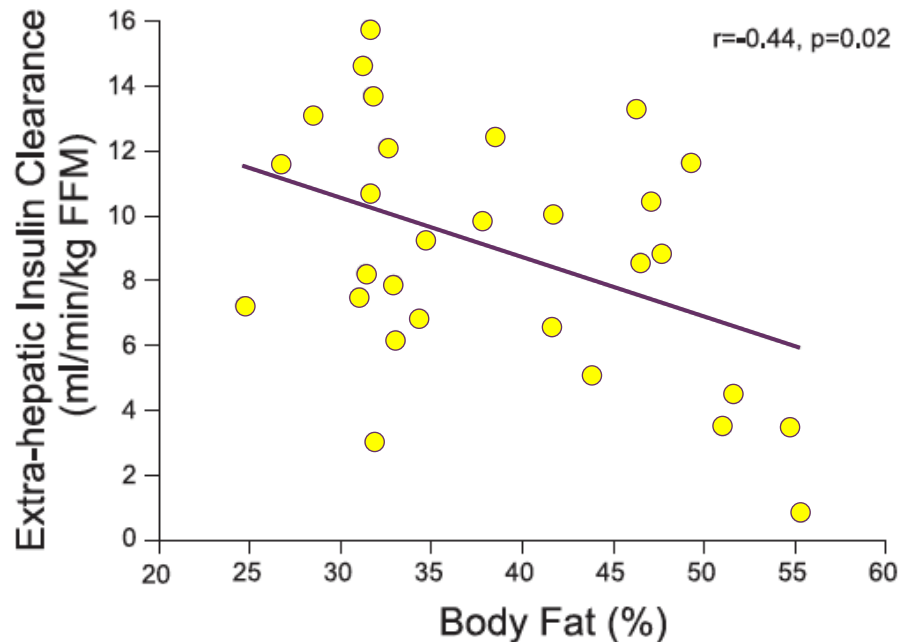
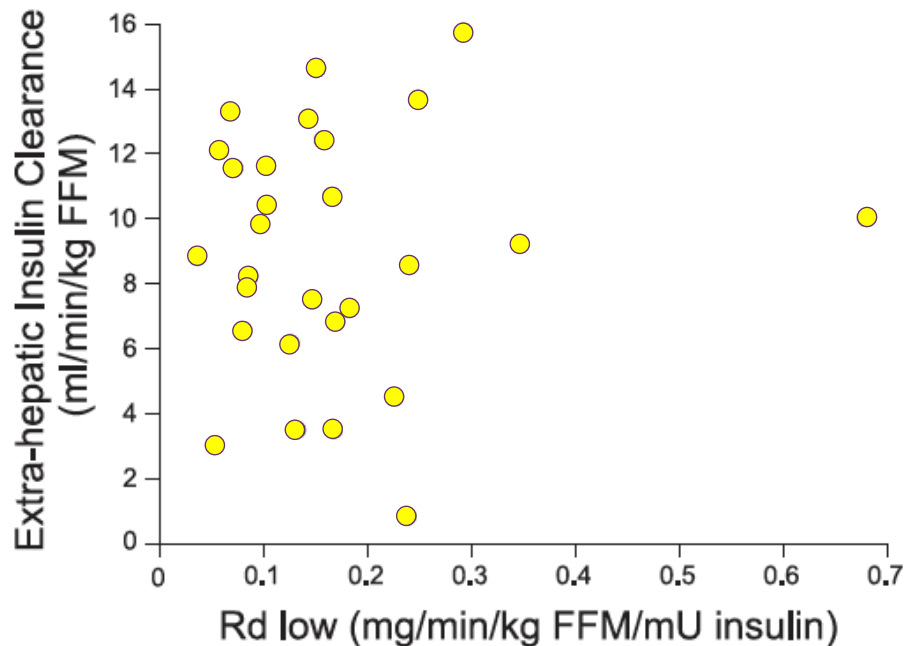
# Introduction of Modelling Approaches for Estimating Insulin Clearance

1. Eaton – J Clin Endocrinol Metab 56:1294-1300; 1983
2. Tura – Am J Physiol 281:E966-E974; 2001
3. Toffolo – Am J Physiol 290:E169-E176; 2006
4. Campioni – Am J Physiol 297:E941-E948; 2009
5. Piccinini – IEEE Trans Biomed Eng 63:1925-1932; 2016
6. Polidori – Diabetes 65:1556–1564; 2016

# Hepatic Insulin Extraction Is Related to Muscle and Adipose Tissue Insulin Sensitivity



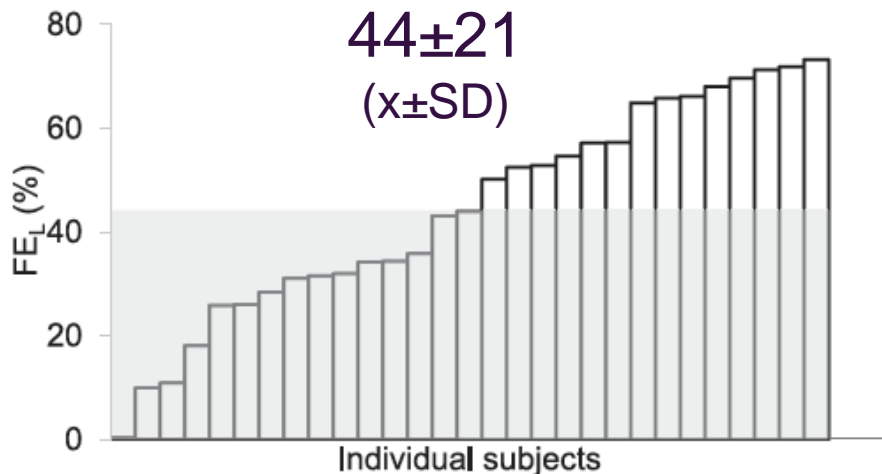
# Extra-Hepatic Insulin Clearance Is Related to Body Fat but Not Muscle Insulin Sensitivity



# Hepatic Insulin Extraction is Lower in African American Women

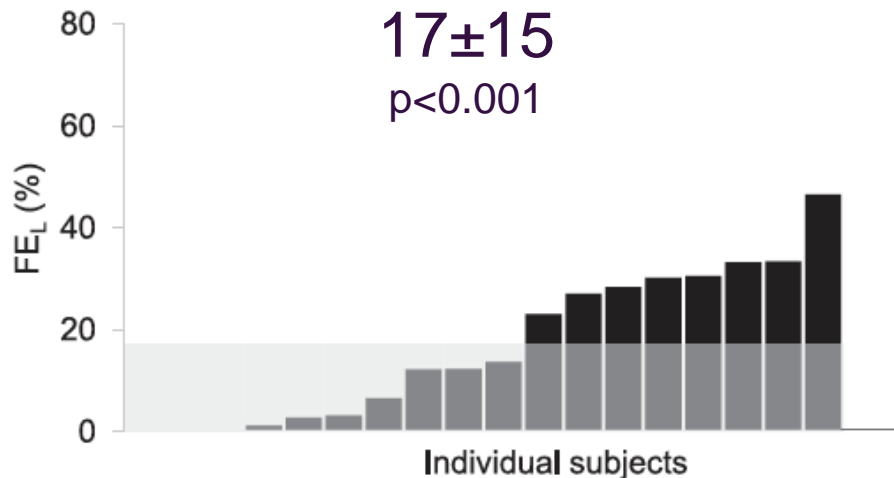
## European American Women

$44 \pm 21$   
( $x \pm SD$ )



## African American Women

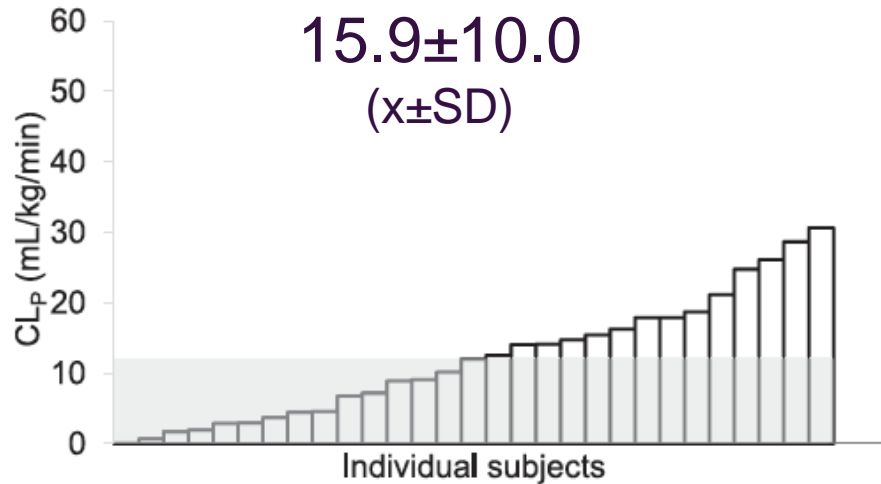
$17 \pm 15$   
 $p < 0.001$



# Extra-Hepatic Insulin Clearance Does Not Differ in European and African American Women

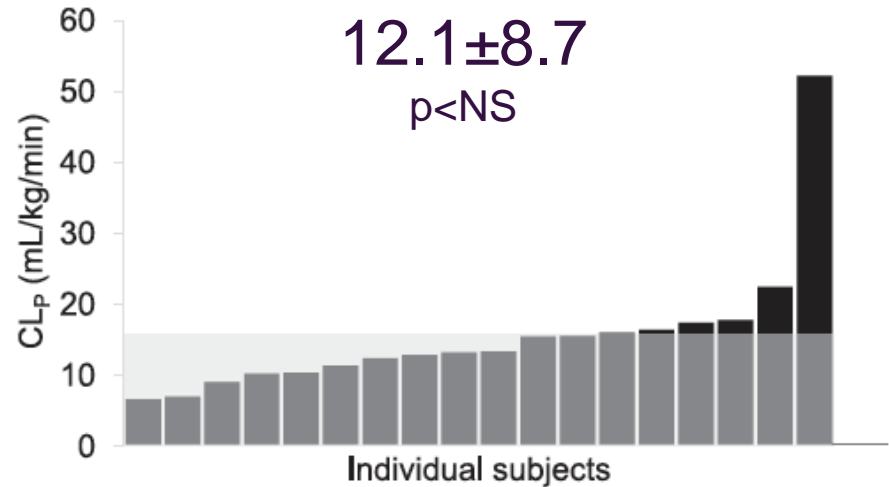
European American  
Women

$15.9 \pm 10.0$   
( $x \pm SD$ )



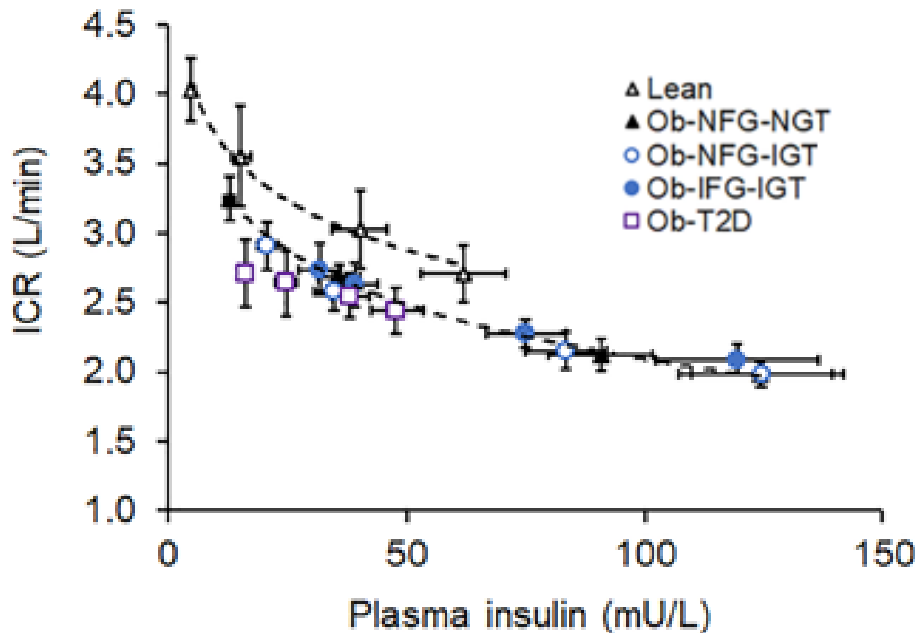
African American  
Women

$12.1 \pm 8.7$   
 $p < NS$

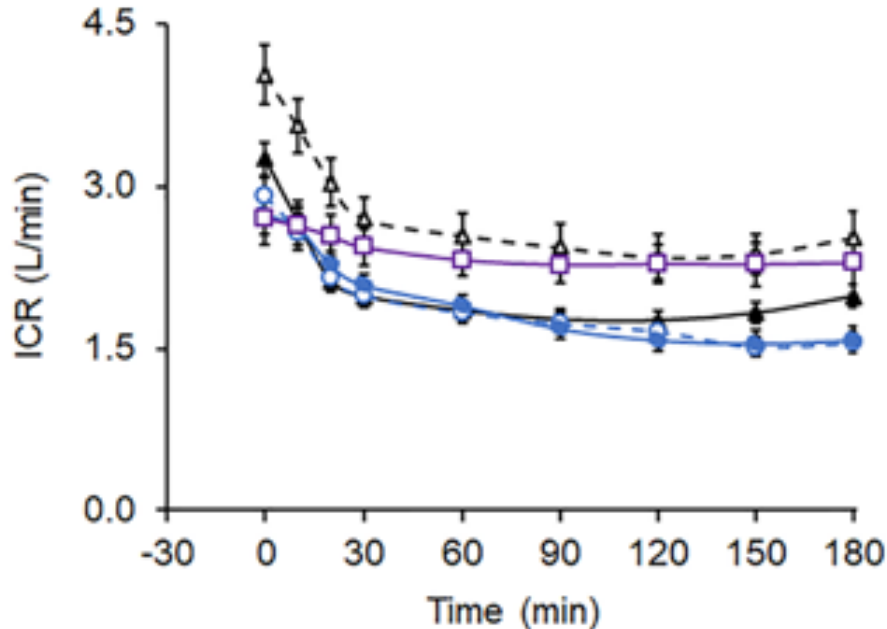


# Whole-Body Insulin Clearance Is Reduced by Obesity but Not by Glucose Tolerance Status

First 30 minutes of OGTT

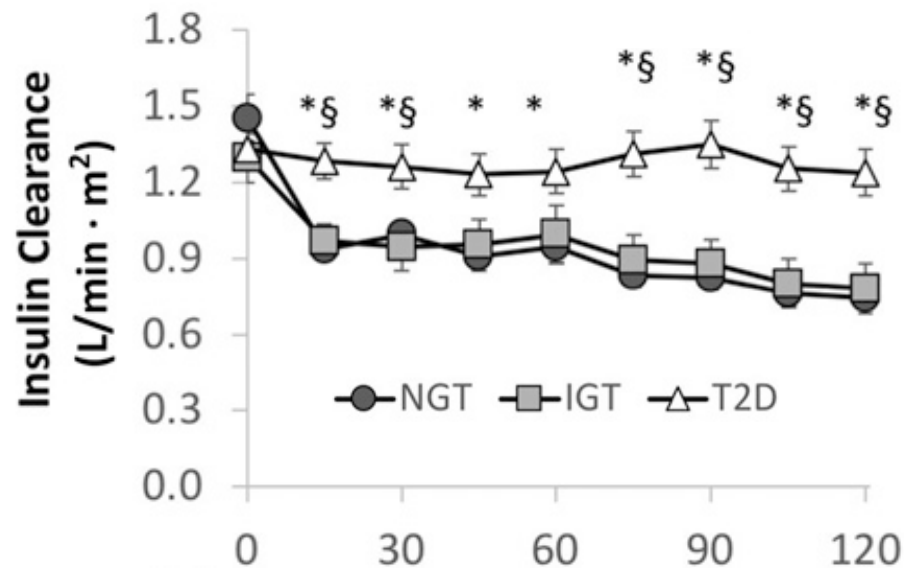


3-hour OGTT

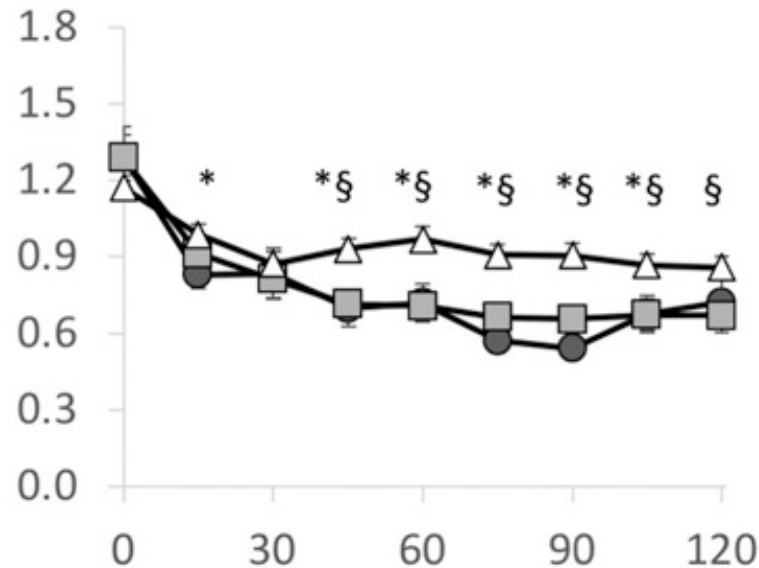


# Suppression of Insulin Clearance During the OGTT Is Impaired in Type 2 Diabetes

## Non-Obese



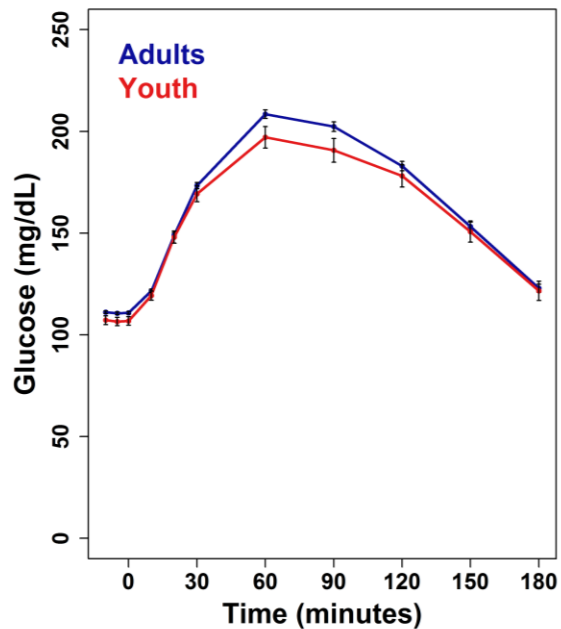
## Obese



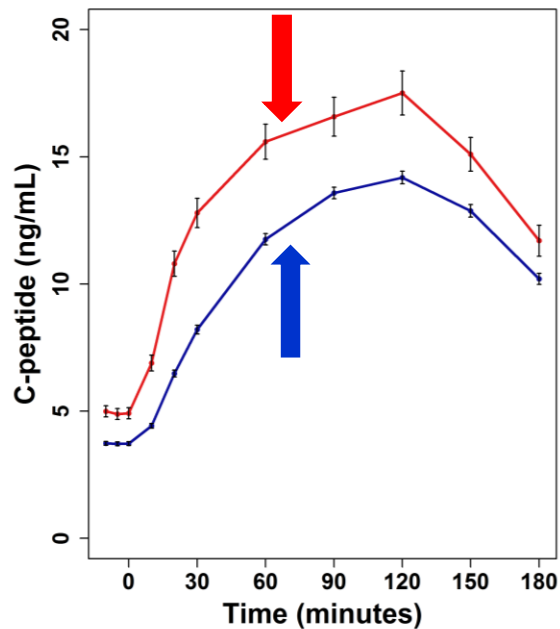


# OGTT Glucose, C-peptide and Insulin Profiles in Youth versus Adults

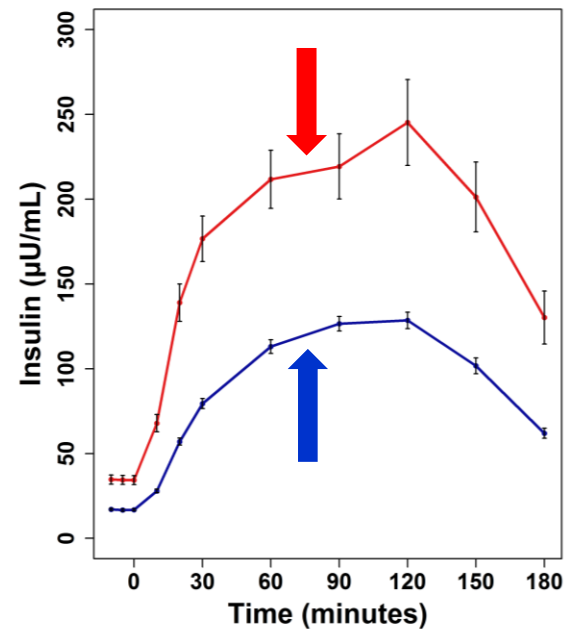
## Glucose



## C-peptide



## Insulin



# Summary

1. Insulin resistance is present in people with IGT and type 2 diabetes.
2. Progressive  $\beta$ -cell dysfunction is the basis for progression from NGT to IGT and then type 2 diabetes. It also explains progressive dysglycemia during glucose-lowering medications.
3. Insulin clearance is decreased in obesity, but does not appear to be a major determinant of  $\beta$ -cell failure.

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# Assessing the Pathophysiological Sequence in the Development of Type 2 Diabetes



|                   |                         |                                |   |
|-------------------|-------------------------|--------------------------------|---|
| Pregnancy history | Genetics<br>Epigenetics | Obesity/body fat<br>Biomarkers | Insulin sensitivity<br>Beta-cell function<br>Insulin clearance<br>Glucose effectiveness |
|-------------------|-------------------------|--------------------------------|---|

# Acknowledgements

Numerous fellows, faculty and colleagues who have helped formulate my thoughts over the years.

Department of Veterans Affairs  
NIH/NIDDK  
American Diabetes Association