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The Beta Cell – Insulin Resistance Connection: A Fat Story?

Eric Ravussin, Ph.D.

18th World Congress Insulin Resistance Diabetes & Cardiovascular Disease;
December 2020

Pennington Biomedical Campus

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Insulin Resistance and β-cell "Performance"

- Natural history of T2DM from prospective clinical investigations (obesity, hepatic glucose production, insulin sensitivity and insulin secretion) among Pima Indians

- Whole body insulin resistance eventually leads to a loss of early phase insulin secretion

- Potential factors leading to a reduction of beta-cell mass (and failure) including:
  - Hyperinsulinemia
  - Glucotoxicty
  - Lipotoxicity
  - Nutrient-induced metabolic stress (Nutri-stress)

Metabolic Abnormalities in Type 2 Diabetes

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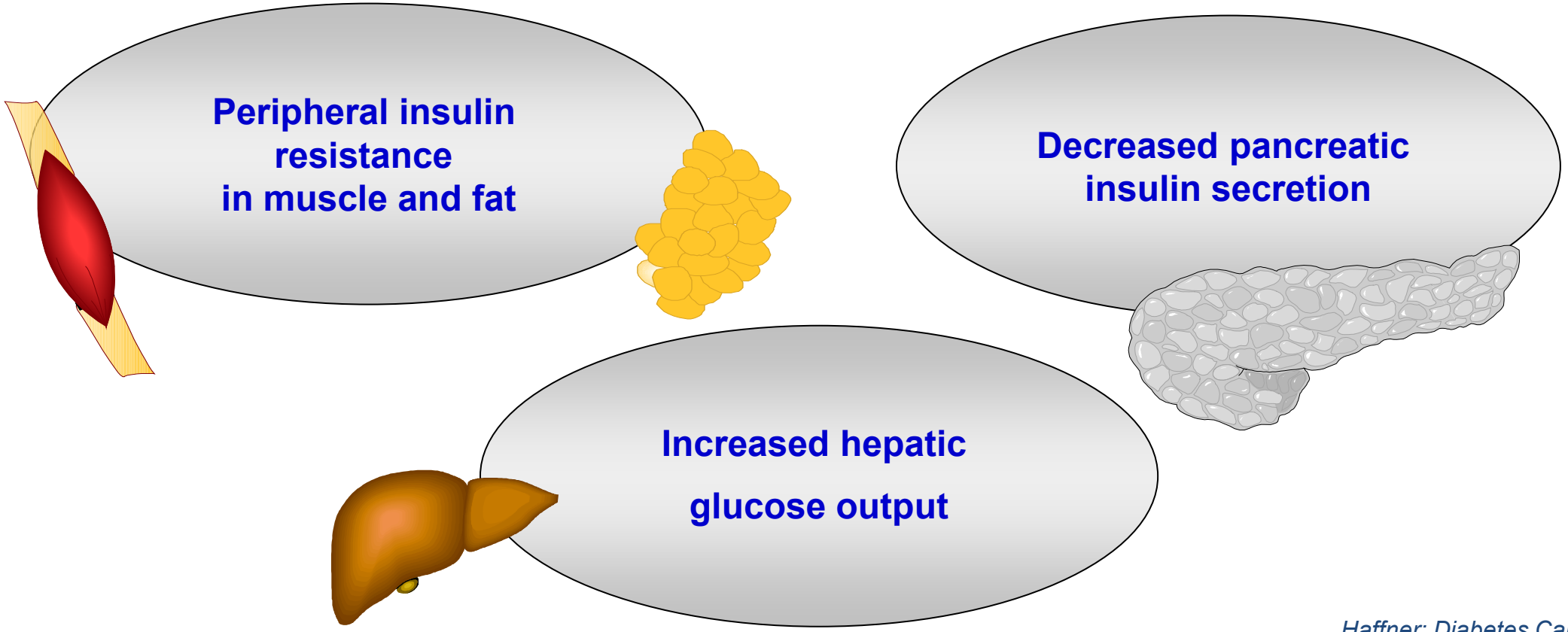
Obesity



Haffner; Diabetes Care 1999

1982-98 Prospective Study of Diabetes in Pima Indians

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PURPOSES

- Identify metabolic predictors of diabetes
- Determine the sequence of metabolic events during the transition from normal glucose tolerance to diabetes
- To assess cellular determinants of insulin resistance and obesity

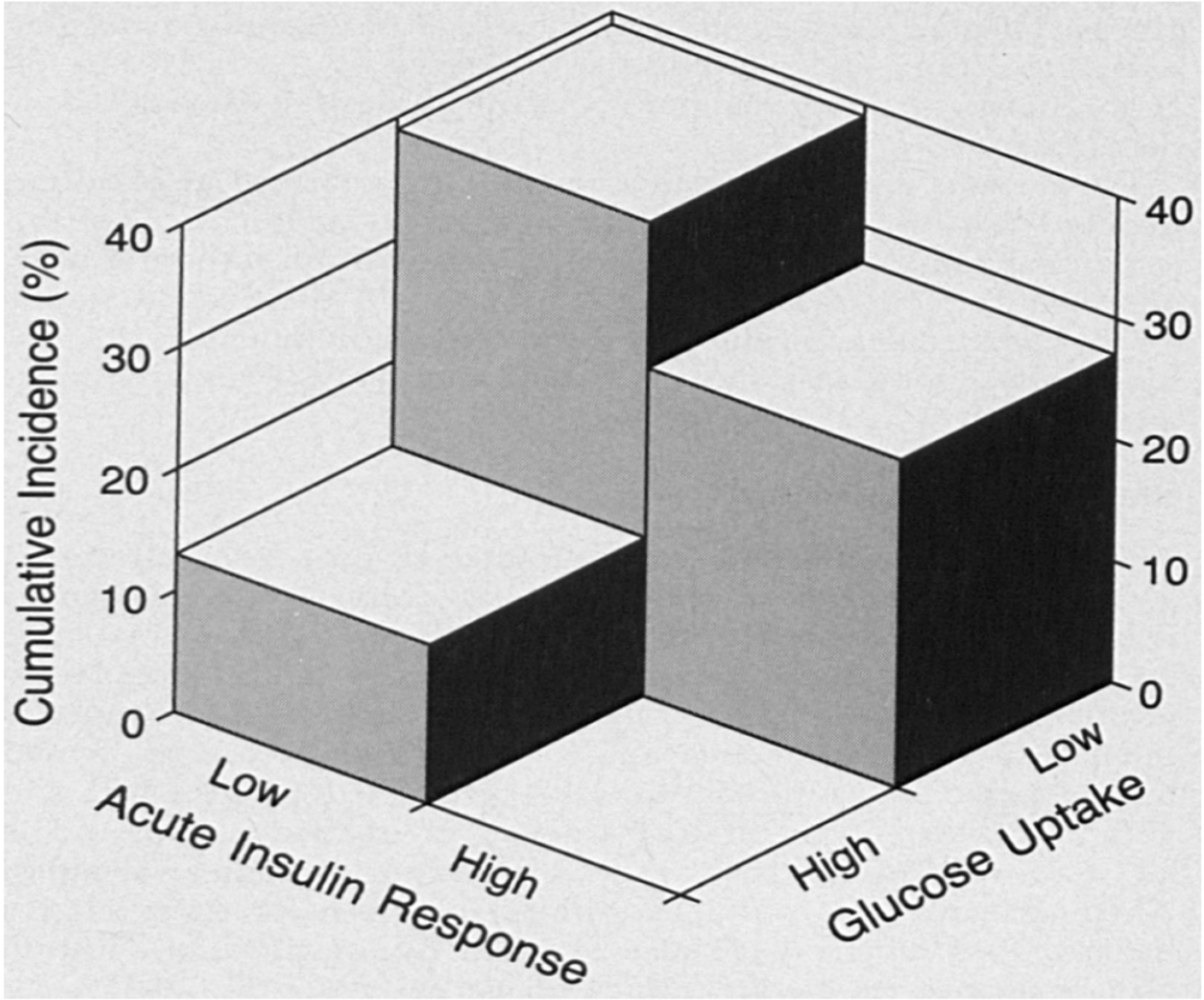
ANNUAL MEASURES

- Anthropometrics & body composition
- Oral glucose tolerance (OGTT)
- Acute insulin response to IV glucose
- Mixed meal test
- Two step hyperinsulinemic euglycemic clamp
- Muscle and adipose tissue biopsies
- Insulin secretory glucose-dose response curve

Metabolic Predictors in T2DM

- Obesity
- Insulin Resistance
- Abnormal Insulin Secretion
- ~~Excess Glucose Production~~

8-y Cumulative Incidence (%) of Type 2 Diabetes in Pima Indians
317 NGT/62 Diabetics



Lillioja S et al; NEJM 1993

Insulin Resistance and β-cell "Performance"

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Natural History of Insulin Secretory Dysfunction

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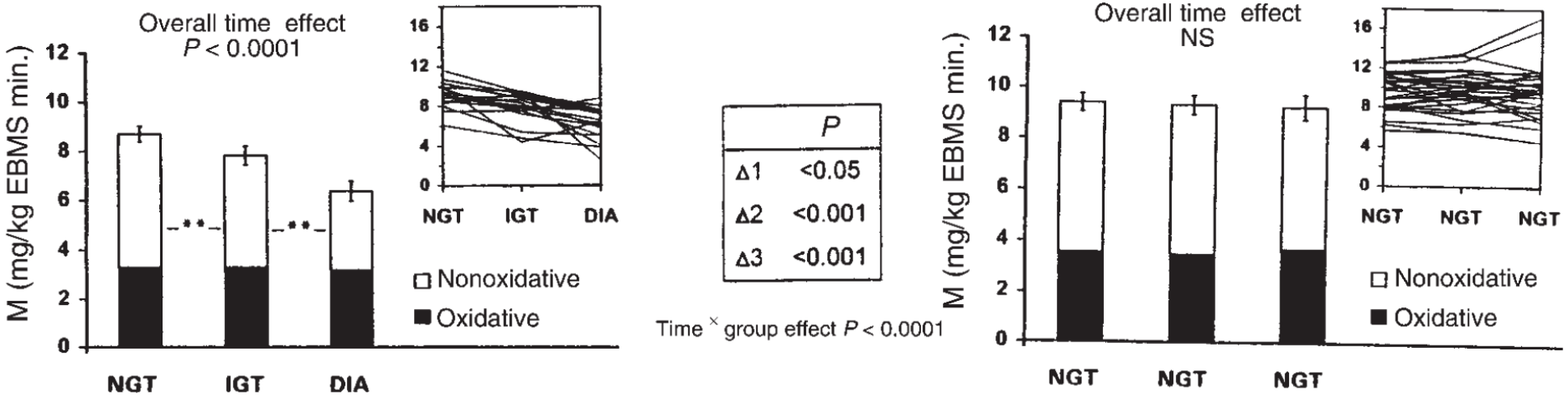
Progressors (N=17) **Non-Progressors (N=31)**

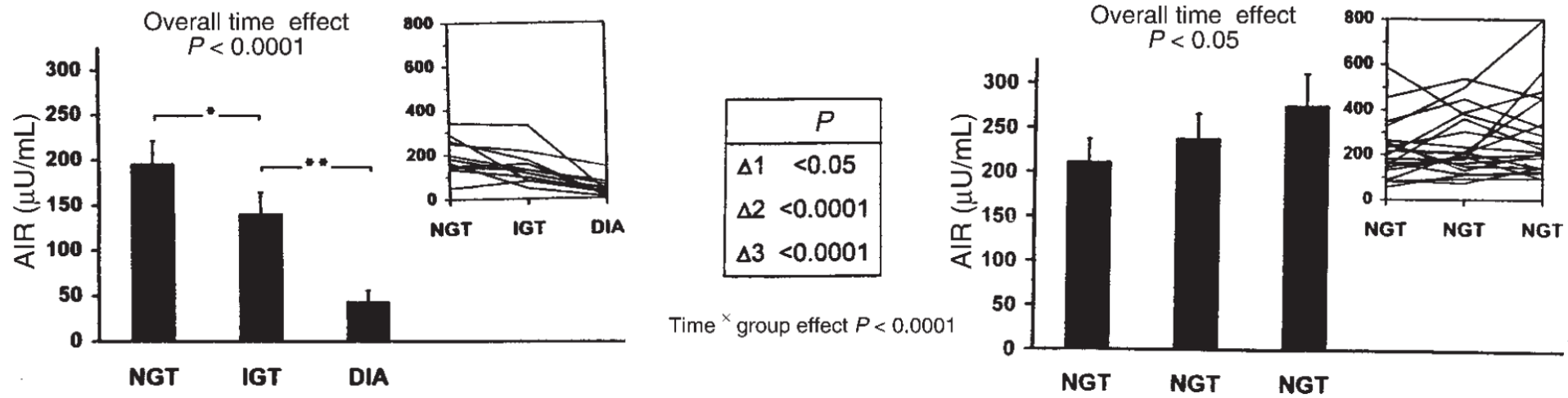
Glucose disposal (M-high)



	P
Δ1	<0.05
Δ2	<0.001
Δ3	<0.001

Time × group effect $P < 0.0001$

Acute insulin response (AIR)



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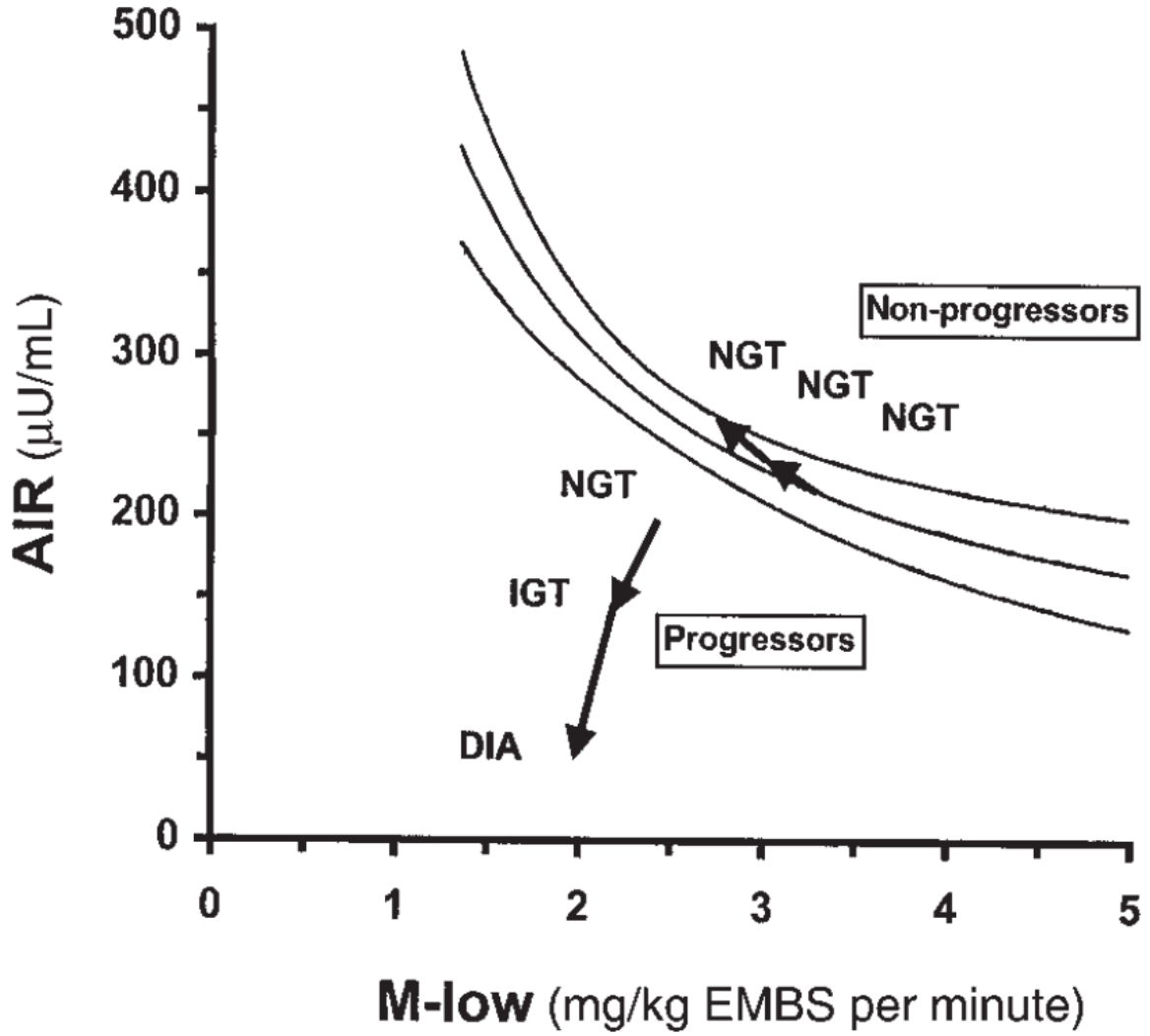
Weyer C et al; JCI 1999

Natural History of Insulin Secretory Dysfunction



Weyer C et al; JCI 1999

Insulin Sensitivity and Secretion in DM-Exposed Offspring

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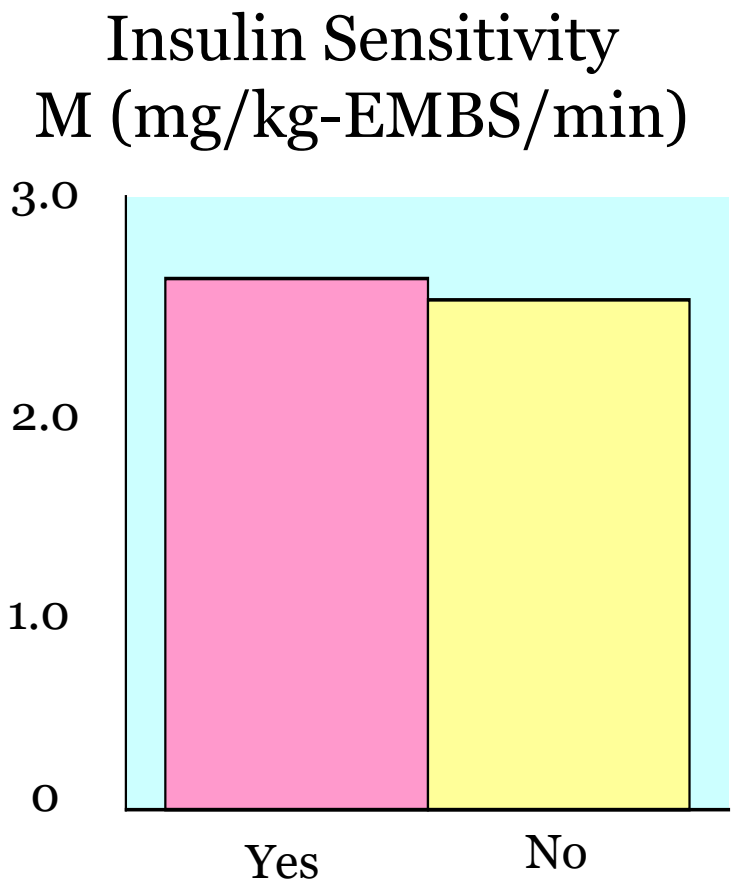

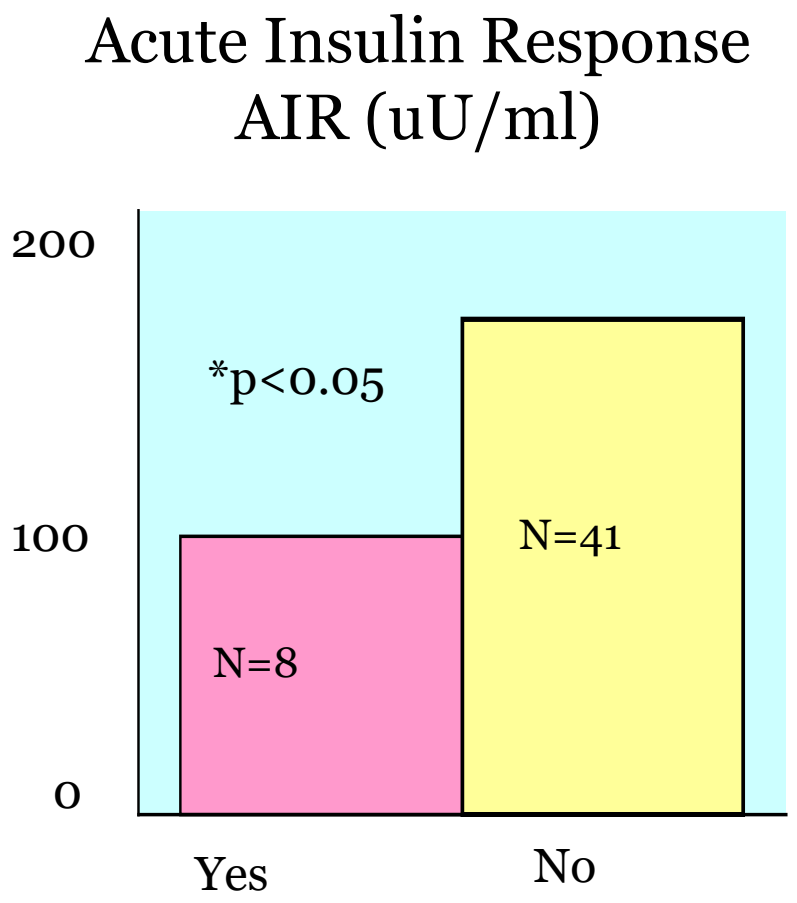

Mother's Diabetes During Pregnancy

Gautier et al; Diabetes 2001

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β-cell Dysfunction: Glucotoxicity? Lipotoxicity? Nutri-Stress ????

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Diabetes Volume 69, March 2020 273

Glucolipotoxicity, β-Cells, and Diabetes: The Emperor Has No Clothes

Gordon C. Weir

Diabetes 2020;69:273–278 | https://doi.org/10.2337/db19-0138

*"Thus, the terms **lipotoxicity** and **glucolipotoxicity** should be used with great caution, if at all, because evidence supporting their importance has not yet emerged……. We are missing the demonstration that the FFA levels existing in obesity and diabetes are in any way damaging to b-cells".*

Diabetes Volume 69, March 2020

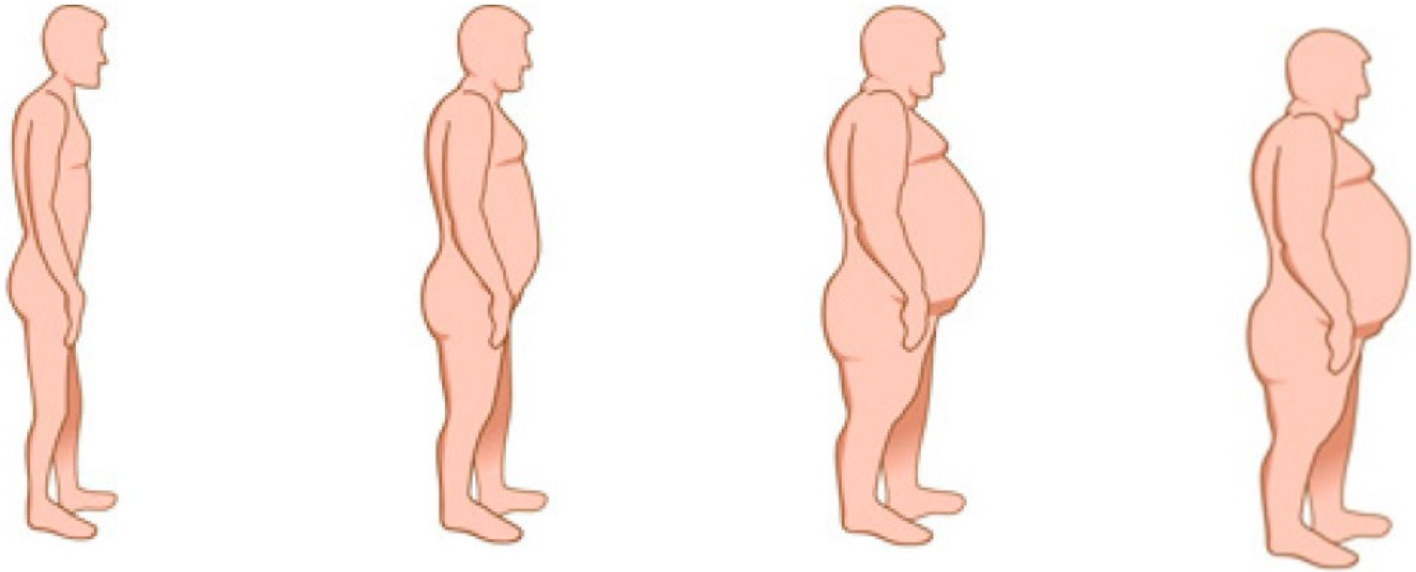
Nutrient-Induced Metabolic Stress, Adaptation, Detoxification, and Toxicity in the Pancreatic β-Cell

Marc Prentki,[1] Marie-Line Peyot,[1] Pellegrino Masiello,[2] and S.R. Murthy Madiraju[1]

Diabetes 2020;69:279–290 | https://doi.org/10.2337/dbi19-0014

"We propose that a more general term should be used for the in vivo situation of overweight-associated type 2 diabetes reflecting both the adaptive and toxic processes to caloric nutrients excess: nutrient-induced metabolic stress or ***"nutri-stress."***

Obesity Increases the Demand for Insulin



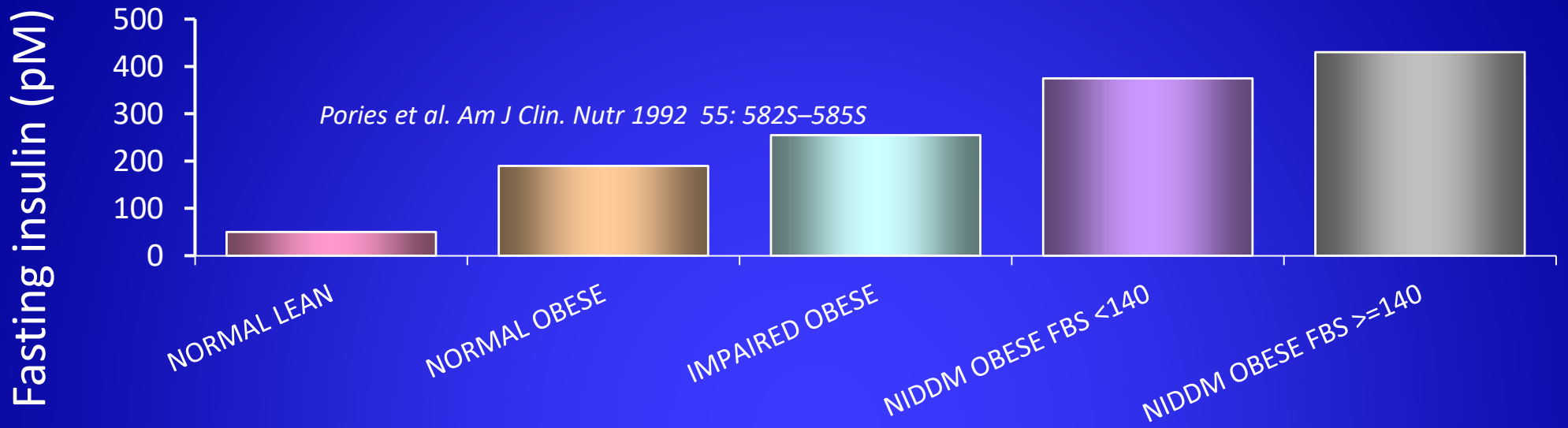
	Lean	Overweight	Obese	Diabetes
Insulin Secretion	+	++	+++	- -

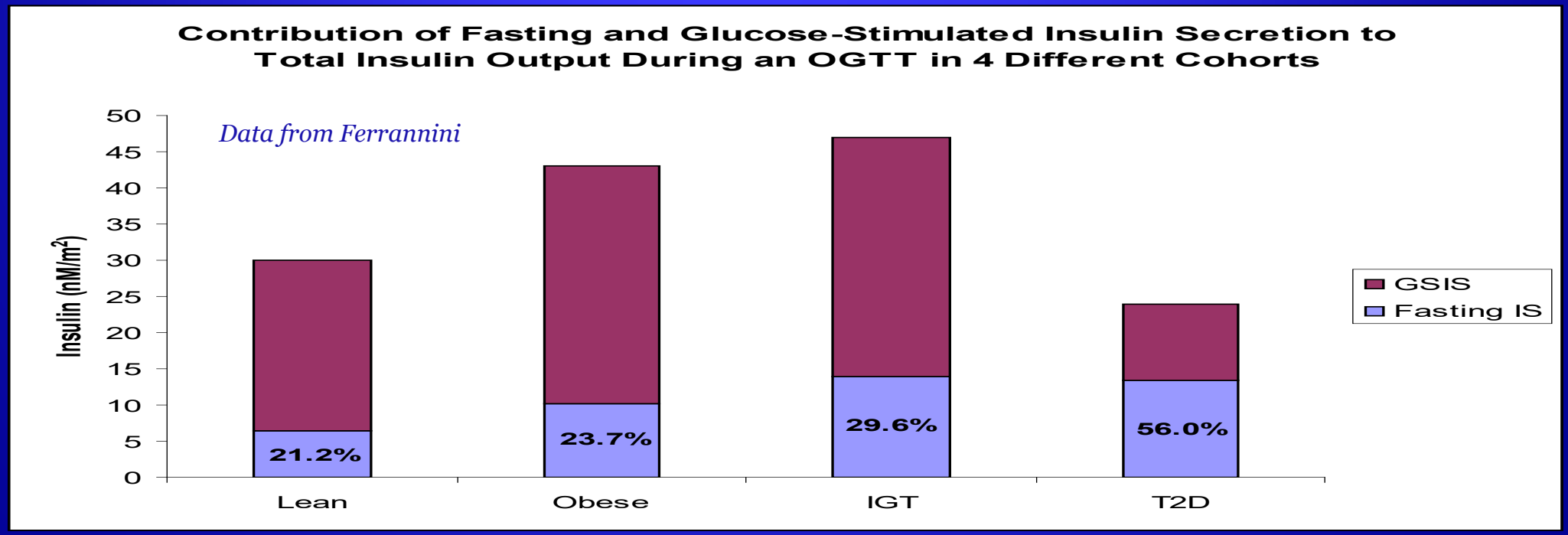
β-cell Dysfunction/ De-differentiation/ Death

- Obesity, insulin resistance, hyperinsulinemia, inflammation & hyperlipidemia coexist
- No evidence that one precedes the others
- Each can cause the others

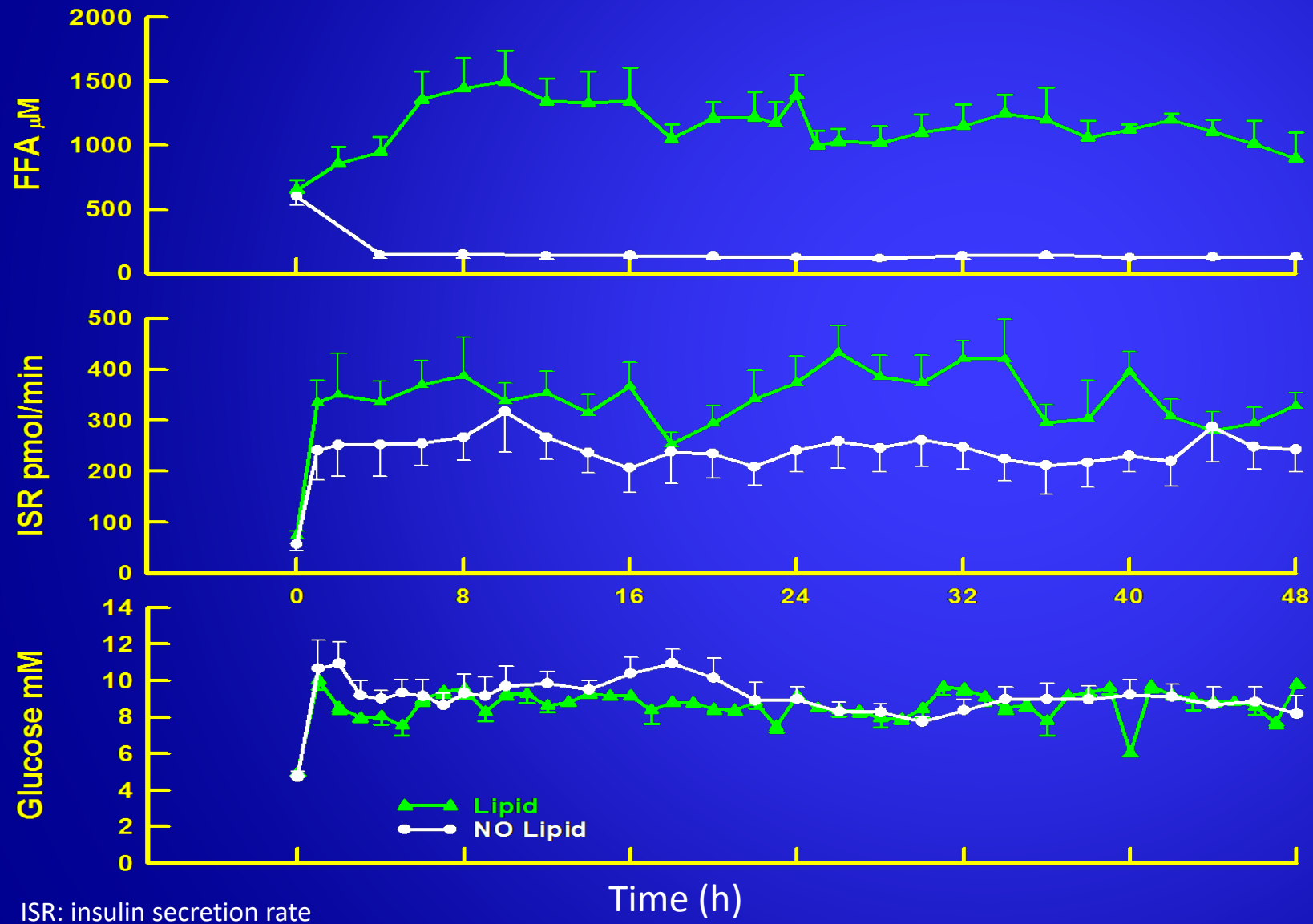
Adapted from Nolan, et al., Diabetes, 2015

Patients with Type 2 Diabetes Have Insulin Levels 900% of Normal





FFA Potentiate Glucose Stimulated Insulin Secretion

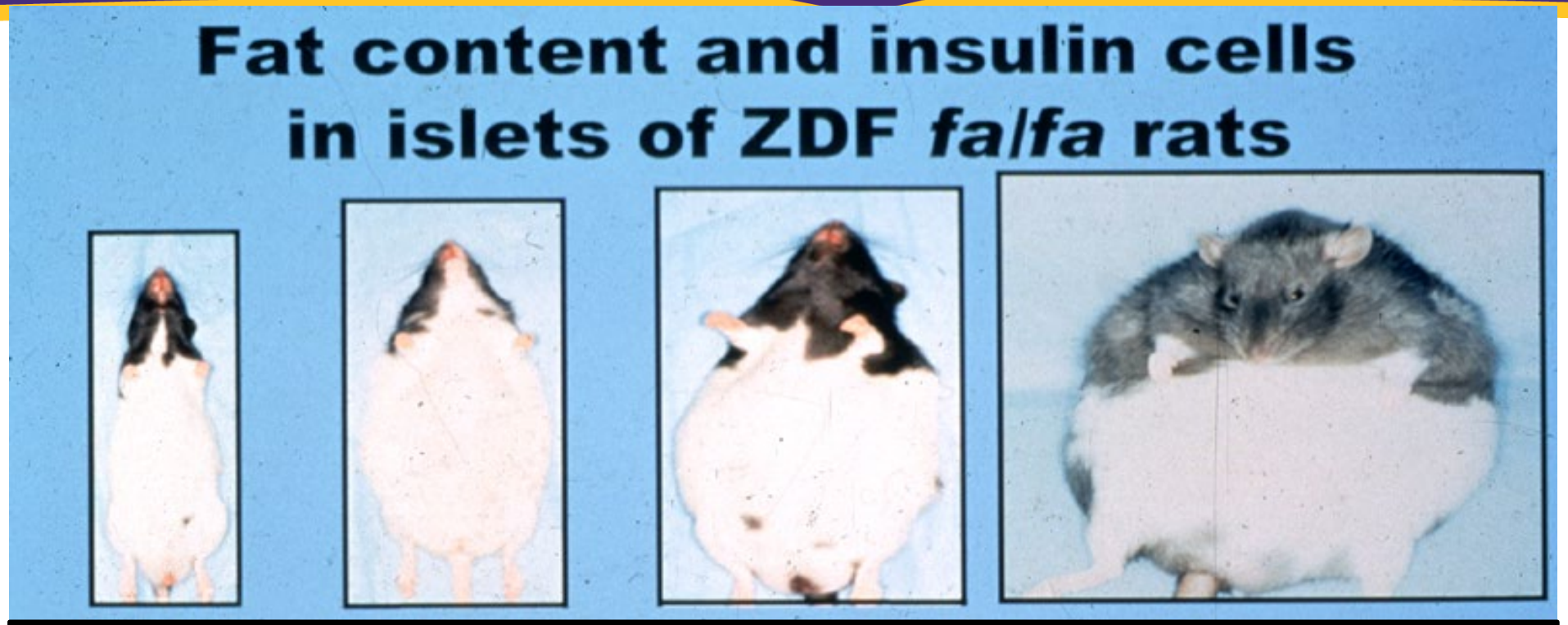


Under hyperglycemic conditions, FFA infusion produces insulin resistance that is compensated for after 24-h by persistent hypersecretion of insulin

ISR: insulin secretion rate

Boden G et al. *Diabetes* 1995 44:1239-1242

Lipid Content and Islet Morphology in from ZDF rats



From Roger Unger

Leukocytes Associated with Islet β-cell Dysfunction in T2DM

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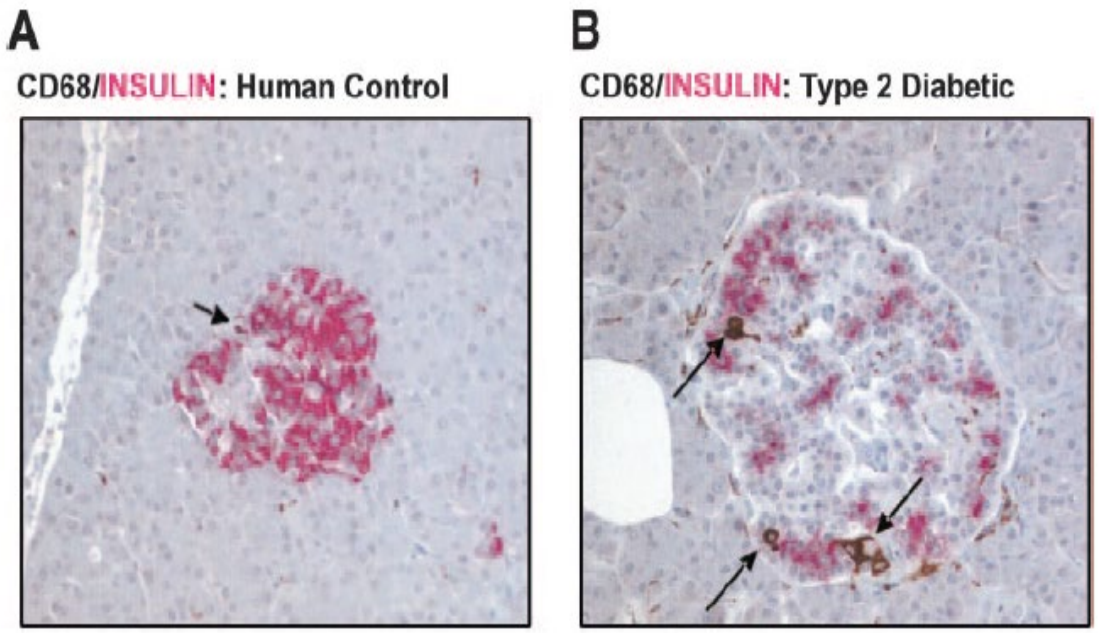
Donath, et al., *Diabetes Care*, 2008



Increased CD68+ cells in Human T2DM

- How does inflammation influence changes in islet mass and function?
- What cytokine signaling pathways are relevant in islet β-cells?

Role of ROS in β-cell Dysfunction

- ROS production occurs in response to excess fuel
  - Excess mitochondrial fuel (NADH) generates ROS when ATP is sufficient
- ROS metabolism stimulates proton leak and H_2O_2 stimulates insulin secretion
- Scavenging ROS inhibits insulin secretion
  - Failure to regulate ROS can cause β-cell dysfunction

Development of β-cell Dysfunction

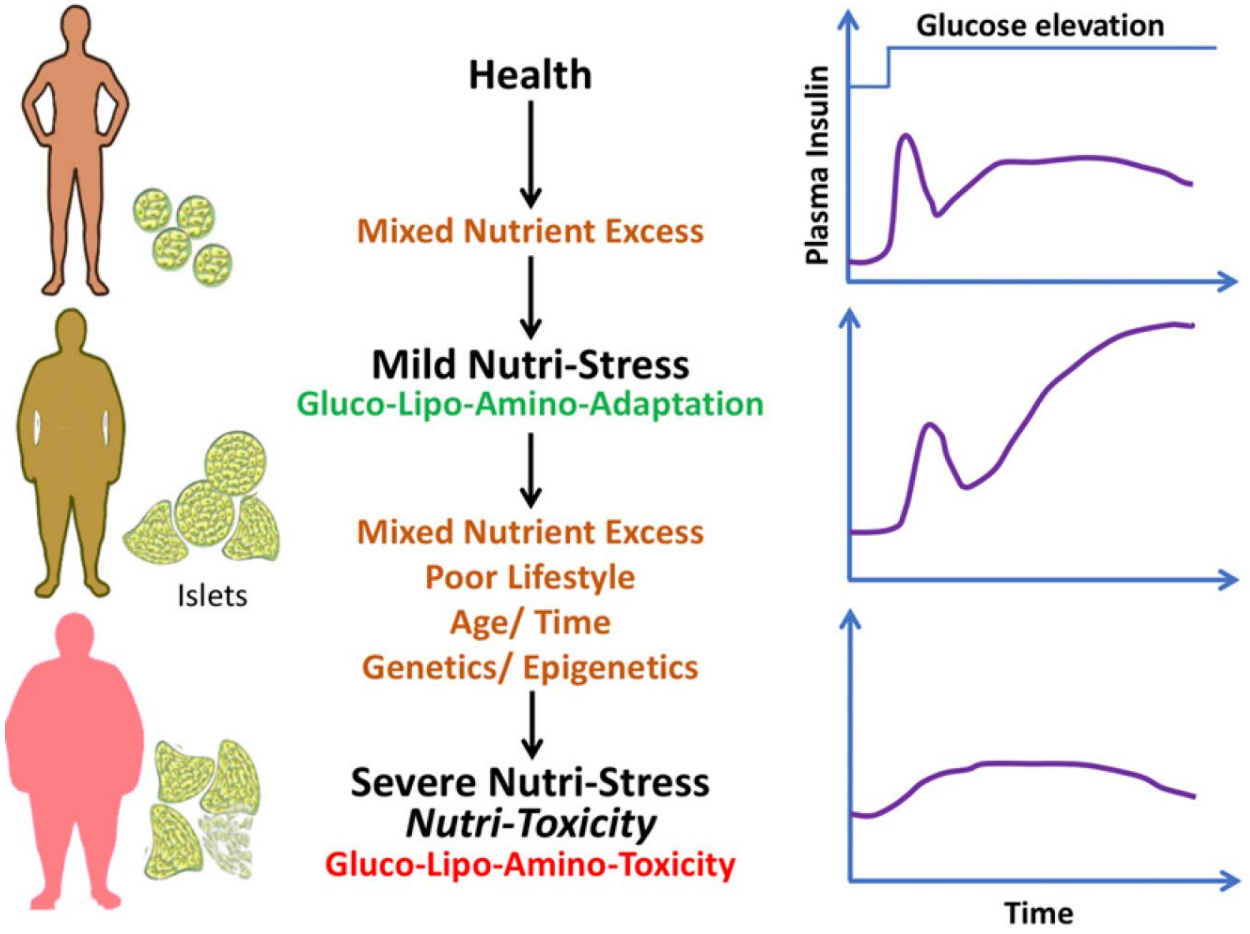
Diabetes Volume 69, March 2020

Nutrient-Induced Metabolic Stress, Adaptation, Detoxification, and Toxicity in the Pancreatic β-Cell

Marc Prentki,[1] Marie-Line Peyot,[1] Pellegrino Masiello,[2] and S.R. Murthy Madiraju[1]

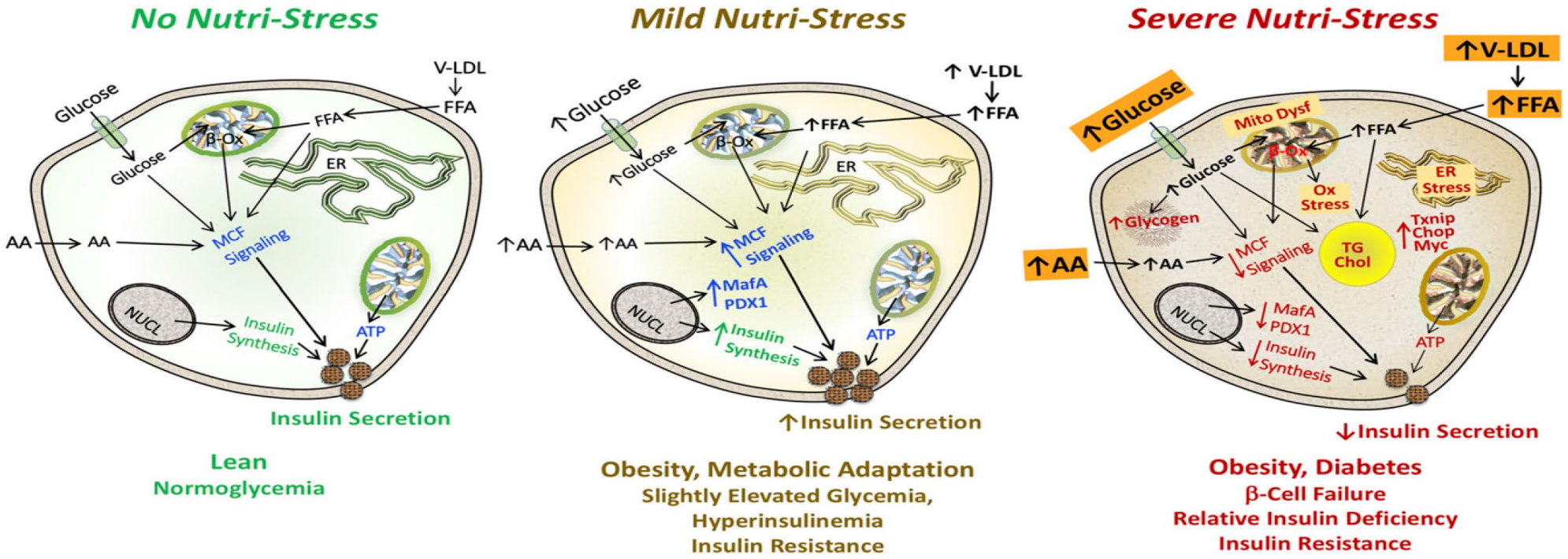
Diabetes 2020;69:279–290 | https://doi.org/10.2337/dbi19-0014

- **Healthy** individuals: Bi-phasic insulin secretion
- Excess fuel (glucose, lipids, AA) cause a **mild nutri-stress** on β-cell resulting in increased basal and second phase insulin secretion by hyperplasia but no cell death
- Prolonged poor lifestyle, age and genetics result in severe nutri-stress or **nutri-toxicity** culminate in β-cell dysfunction and eventually failure with marked reduction in β-cell secretory response



Potential Pathways from Healthy to Failed β-Cell

Pancreatic *β*-cell responds to glucose, FFA, and amino acid (AA) stimulation by producing metabolic coupling factors (MCF) through various pathways in cytosol, ER, and mitochondria playing a critical role in optimal insulin secretion.



Obesity with *β*-cell failure and diabetes will result when there is severe chronic nutri-stress that overwhelms the *β*-cell metabolic machinery. Under these conditions, there is mitochondrial and ER dysfunction causing oxidative and ER stress, accompanied by reduced MCF production and decreased insulin synthesis and secretion.

Prentki et al; Diabetes 69; 2020

Take Home Message: Insulin Resistance and Failed β-Cell

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- Insulin resistance drives insulin secretion
- Those who cannot keep up with insulin secretion develop T2DM
- Many T2DM-associated SNPs have a genetic contribution to pancreatic β-cell function
- High glucose, hyperinsulinemia, high lipids and excess AA increase oxidative/ER stress leading to β-cell failure

- Nutri-stress overwhelms the β-cell metabolic machinery leading to decreased insulin synthesis and secretion.