PATHOGENESIS OF T2DM: ROLE OF INSULIN RESISTANCE

Ralph A. DeFronzo, MD
Professor of Medicine
Chief, Diabetes Division
UTHSC
San Antonio, Texas
THE TRIUMVIRATE

Impaired Insulin Secretion

Hyperglycemia

Increased HGP

Decreased Glucose Uptake

DeFronzo RA, Diabetes 37:667-687, 1988
Natural History of T2DM

Mean Plasma Insulin During OGTT (µU/ml)

Mean Plasma Glucose During OGTT (mg/dl)

Insulin-Mediated Glucose Uptake (mg/m²·min)

DeFronzo & Felber
Diabetes 37:667-687, 1988
Metabolism 39:1068-75, 1990
Beta cell failure occurs much earlier in the natural history of type 2 diabetes and is more severe than previously appreciated.
<table>
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<th>SUBJECTS</th>
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<td>NGT</td>
<td>318</td>
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<td>IGT</td>
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**METHODS:** OGGTT and Insulin Clamp

PLASMA GLUCOSE AND INSULIN AUC

Glucose AUC (mmol/L • 120 min)

Insulin AUC (pmol/L • 120 min)

CON Q1 Q2 Q3 Q4

IGT T2DM

CON Q1 Q2 Q3 Q4

IGT T2DM
INSULIN SECRETION / INSULIN RESISTANCE (DISPOSITION) INDEX DURING OGTT

Lean

Obese

NGT

IGT

T2DM

2-Hour PG (mg/dl)
The Triumvirate

- Impaired Insulin Secretion
- Hyperglycemia
- Decreased Glucose Uptake

Increased HGP

Decreased Glucose Uptake

DeFronzo RA, Diabetes 37:667-687, 1988
INSULIN RESISTANCE

Fasting State

Insulin-Stimulated State
EFFECT OF INSULIN ON HEPATIC GLUCOSE PRODUCTION IN T2DM

Hepatic Glucose Output (mg/m²-min)

Portal Insulin Conc (µU/mL)

T2DM

CON
BASAL HEPATIC GLUCOSE PRODUCTION (HGP) IN T2DM: RELATIONSHIP WITH FASTING PLASMA GLUCOSE (FPG)

DeFronzo et al, Metabolism 38:387-395, 1989
INSULIN RESISTANCE

Fasting State

Insulin-Stimulated State
INSULIN CLAMP TECHNIQUE FOR QUANTITATION OF INSULIN SENSITIVITY

“M” = Glucose infusion Rate = Glucose Metabolized
INSULIN-MEDIATED GLUCOSE UPTAKE IS REDUCED IN T2DM

DeFronzo et al, JCI 63:939-46, 1979; JCI 76:149-55, 1985
INTRACELLULAR GLUCOSE METABOLISM

Glucose

Glucose 4 Transporter

Glucose

HK II

Glucose-6-P

Glycogen Synthase

Pyruvate Dehydrogenase

Glycogen

Glucose Oxidation
Characterized by multiple intramyocellular defects in insulin action:

- impaired glucose transport
- reduced glycogen synthesis
- decreased glucose oxidation

Proximal defects in the insulin signal transduction system play a paramount role in the muscle insulin resistance
SYNDROME OF INSULIN RESISTANCE

- Obesity
- Diabetes
- Hypertension
- Dyslipidemia
- Increased PAI-1
- Endothelial Dysfunction
- ASCVD
- Hyperinsulinemia

**INSULIN RESISTANCE**
INSULIN-STIMULATED GLUCOSE UPTAKE IN T2DM AND OBESITY

DeFronzo RA, Diabetes 37:667-687, 1988

Glucose Uptake (mg/m^2 min)

- CONTROL
- NORMAL WEIGHT DIABETIC
- OBESE NON-DIABETIC

* p<0.001
** P < 0.01
WHAT DO HYPERTENSION AND DYSLIPIDEMIA HAVE IN COMMON WITH TYPE 2 DIABETES MELLITUS AND OBESITY?
INSULIN SENSITIVITY IN THE IRS

Glucose Uptake (mg/m²-min)

CON
Lean T2DM
Obese NGT
HTN
Hyper-Trigly

* p < 0.001 vs CON
** p < 0.01 vs CON
WHAT DOES CORONARY ARTERY DISEASE HAVE IN COMMON WITH T2DM, OBESITY, DYSLIPIDEMIA, AND HYPERTENSION?
INSULIN SENSITIVITY IN THE IRS

Glucose Uptake (mg/m²-min)

* p < 0.001 vs CON
** p < 0.01 vs CON

Bressler & DeFronzo, Diabetologia 39:1345-50, 1996

CON
Lean
T2DM
Obese
NGT
HTN
Hyper-
Trigly
CAD
MULTIPLE PROSPECTIVE EPIDEMIOLOGIC STUDIES HAVE DEMONSTRATED THAT BOTH IR AND IRS PREDICT CVD, AS WELL AS FUTURE DIABETES (Botnia, Verona, Framingham, SAHS, Bruneck, IRAS)
ASSOCIATION BETWEEN HOMA-IR AND 8-YEAR INCIDENCE OF CVD IN NON-DIABETIC SUBJECTS IN SAHS (187 events in 2,569 subjects)

Hanly, *Diabetes Care* 25:1177, 2002

Adjusted for age, sex, BP, LDL, HDL, TG, smoking, exercise, waist circum.
PREDICTIVE (%) VALUE OF FRAMINGHAM CARDIOVASCULAR RISK ENGINE IN MEN

D'Agostino RB et al, JAMA 286:180-87, 2001

UNEXPLAINED RISK = 31%

PERCENT (%)

FHS  ARIC  ARIC  FHS  HHP  PR  SHS  CHS  White

White (M)  White  Black  White (F)  Japanese Amer  Hispanic  Native Amer  White  69%

MEAN
MOLECULAR ETIOLOGY OF THE INSULIN RESISTANCE SYNDROME
INSULIN SIGNAL TRANSDUCTION SYSTEM IN T2DM HUMANS

INSULIN SIGNAL TRANSDUCTION SYSTEM IN T2DM HUMANS

INSULIN Receptor

Plasma Membrane

Insulin

Glucose

GLUT 4

Artery

IRS-1

p 110

Akt

PI-3-Kinase

MAP kinase

Inflammation

Cell Growth & Proliferation

Atherosclerosis

EFFECT OF INSULIN ON INSULIN SIGNAL TRANSDUCTION IN NORMAL GLUCOSE TOLERANT, INSULIN RESISTANT OFFSPRING OF TWO DIABETIC PATIENTS (FH+)

Pratipanawatr et al, Diabetes 50: 2572-78, 2001

% of insulin-stimulated value in FH-

IR-PY

FH− FH+

IRS-1-PY

FH− FH+

PI3K-IRS-1

FH− FH+

r=0.57, p<0.01 vs Rd

Pratipanawatr et al, Diabetes 50: 2572-78, 2001
EFFECT OF INSULIN ON INSULIN SIGNAL TRANSDUCTION IN NORMAL GLUCOSE TOLERANT, INSULIN RESISTANT OFFSPRING OF TWO DIABETIC PARENTS (FH+)

% of insulin-stimulated value in FH-

ERK Activity

ERK Phosphorylation
INSULIN SIGNAL TRANSDUCTION SYSTEM IN T2DM HUMANS

Insulin Receptor → Insulin → PI-3-Kinase → Akt → GLUT 4

Shc → MAP kinase → Inflammation

Cell Growth & Proliferation
Atherosclerosis

INSULIN SIGNAL TRANSDUCTION SYSTEM IN T2DM HUMANS: EFFECT OF TZDs

LIPOTOXICITY, INSULIN RESISTANCE, AND ASCVD

- Elevated plasma FFA
- Increased tissue fat content
- Altered fat topography
- Adiposopathy
ALTERED FAT TOPOGRAPHY AND ECTOPIC FAT DEPOSITION IN T2DM

DeFronzo RA et al, JCEM 89:463-478, 2004
CONCLUSIONS

• Insulin resistance is a characteristic feature of T2DM and all components of the insulin resistance (metabolic) syndrome

• The molecular etiology of the insulin resistance is associated with the activation of pathways involved with the development of atherosclerosis
CONCLUSIONS

- Lipotoxicity plays a central role in the development of insulin resistance accelerated ASCVD observed in individuals with the metabolic syndrome, type 2 diabetes, and obesity.