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Pathogenesis of Type 2 Diabetes Mellitus

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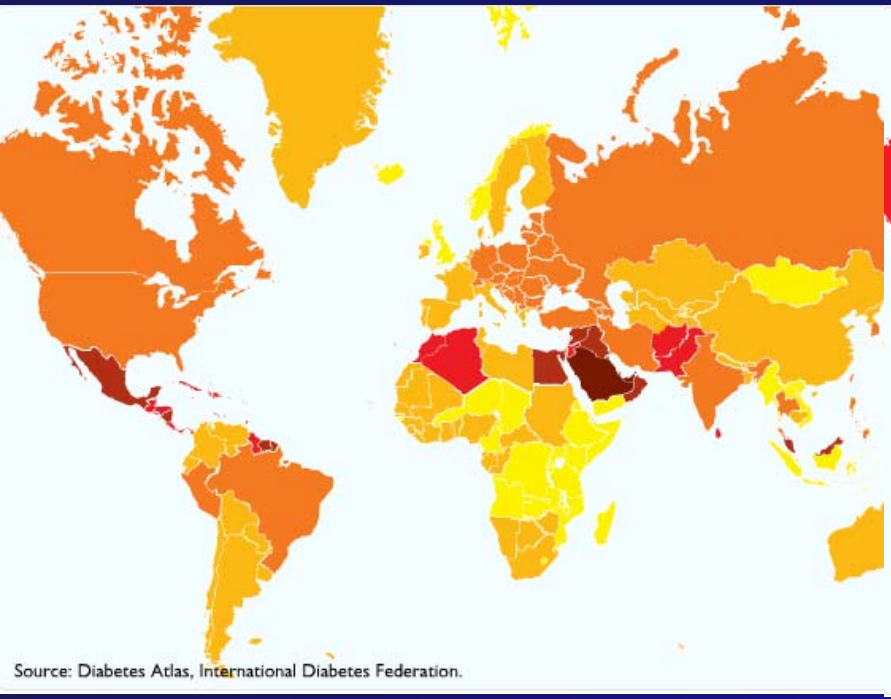
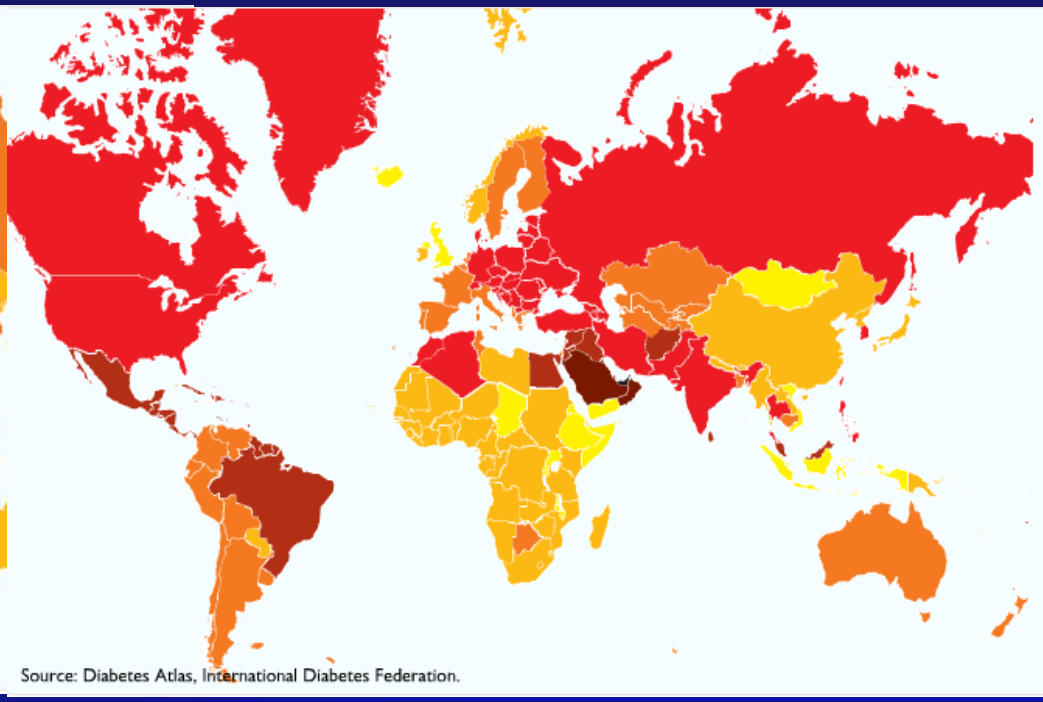
Thessaloniki, 8-9 May 2009

Diabetes: serious, widespread disease

	1995	2000	2007
Type 1	3.5 million	4.4 million	5.5 million
Type 2	114.8 million	146.8 million	240.5 million
TOTAL	118.4 million	151.2 million	246 million

Prevalence of Diabetes





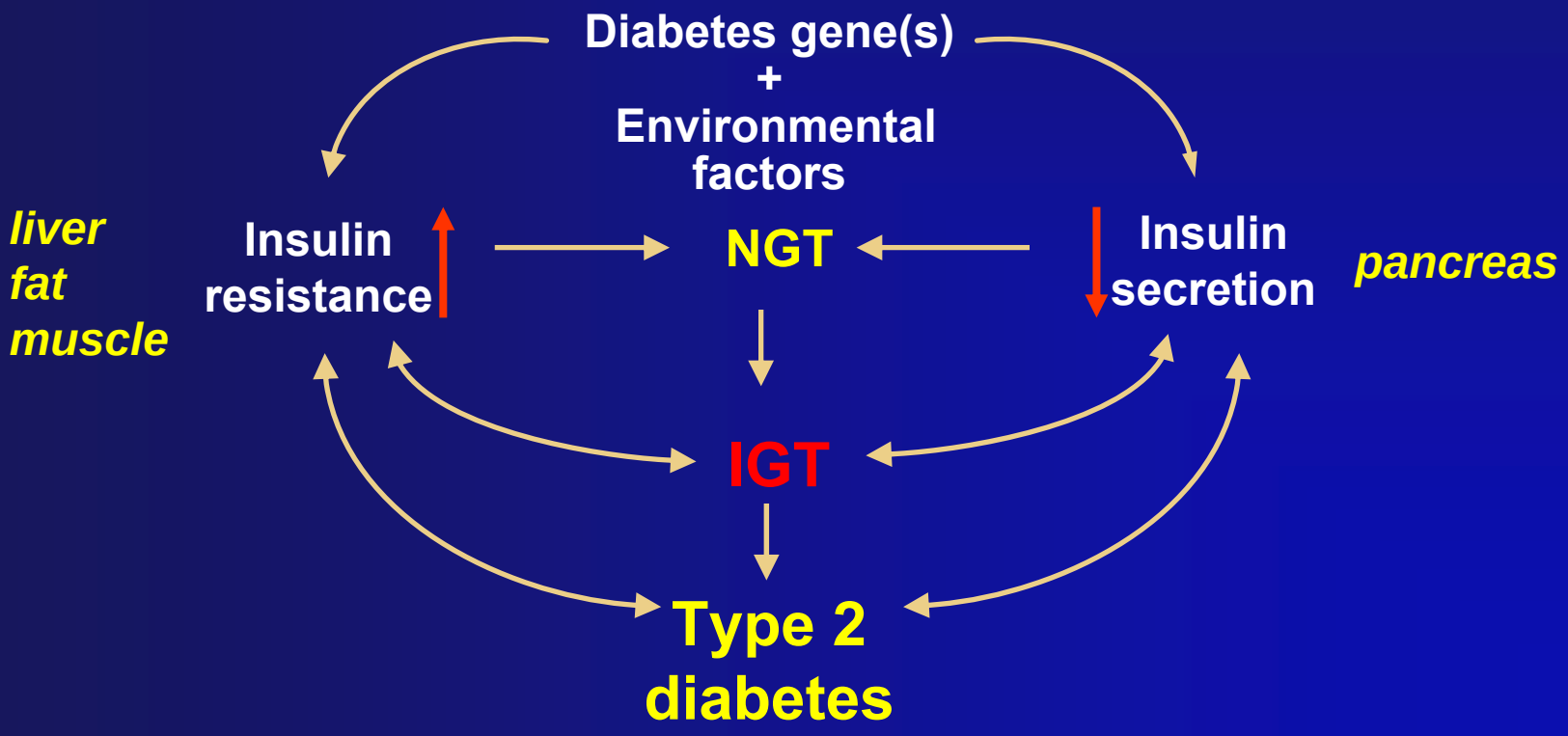
2007 **2025**

No Data	6% – 8%	14% – 20%
< 4%	8% – 10%	> 20%
4% – 6%	10% – 14%	

Source: International Diabetes Federation (IDF) http://www.eatlas.idf.org/

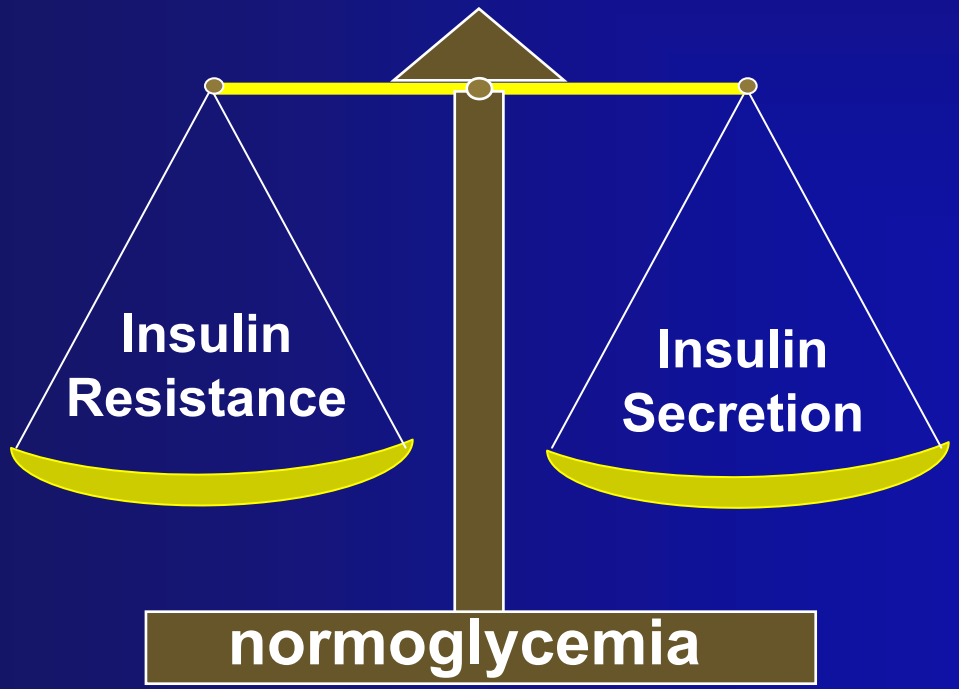
Natural History of T2DM

In the natural history of type 2 diabetes (T2DM), individuals progress from normal glucose tolerance (NGT) to impaired glucose tolerance (IGT) to overt T2DM

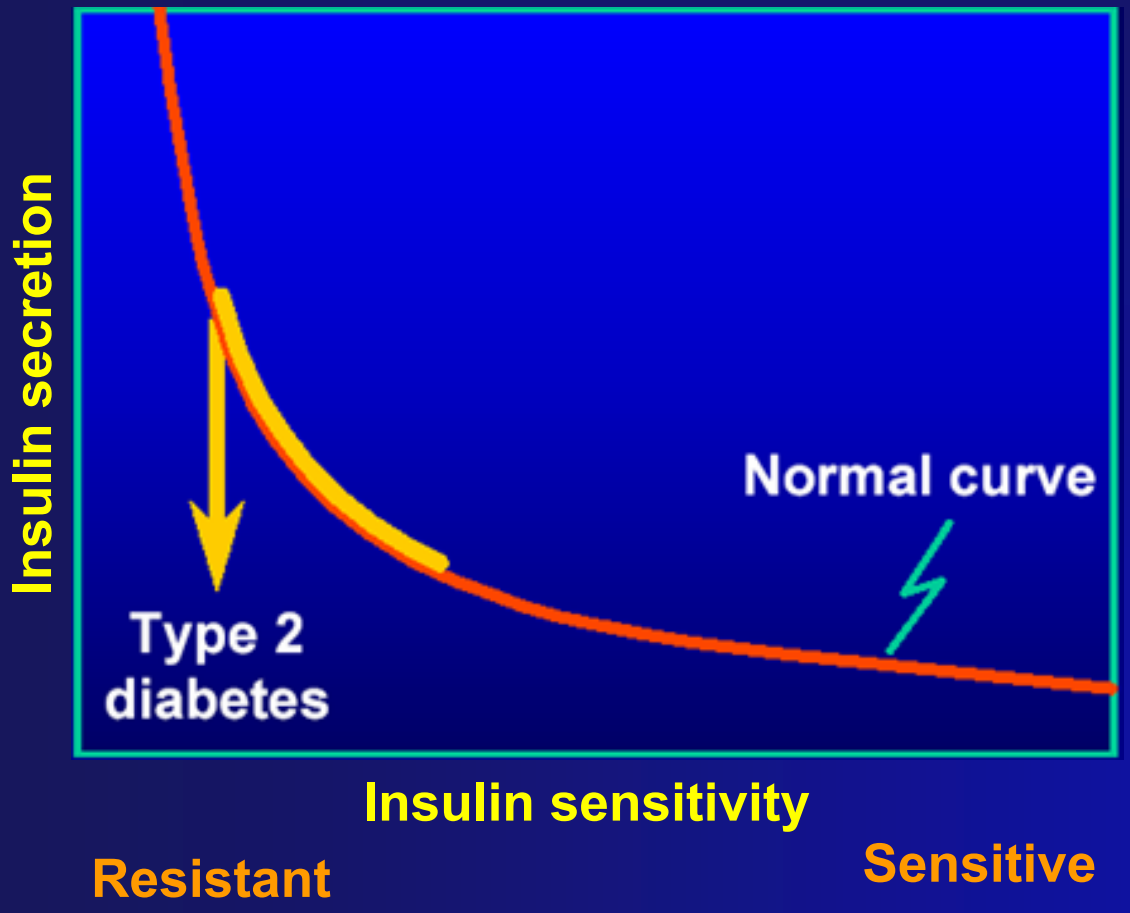


Natural History of T2DM

- It is widely recognised that in the pathogenesis of glucose intolerance and postprandial hyperglycemia both insulin resistance and beta-cell dysfunction are important.



The dynamic interaction between insulin secretion and insulin sensitivity is essential to the maintenance of NGT

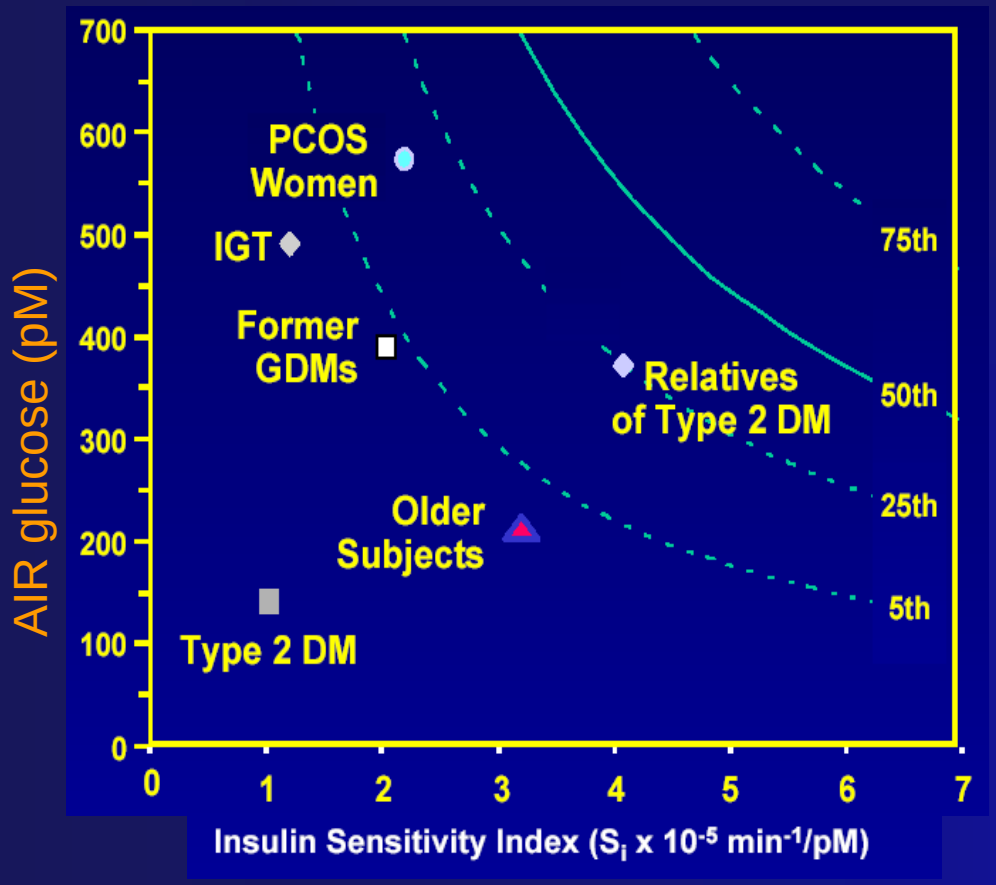


As long as the β-cell is able to secrete sufficient amounts of insulin to offset the severity of insulin resistance, glucose tolerance remains normal.

As the β-cell fails, demands exceeds insulin secretion and type 2 diabetes develops

Bergman RN *Diabetes* 1989; 38:1512-15

Type 2 Diabetes = "Falling off the curve"

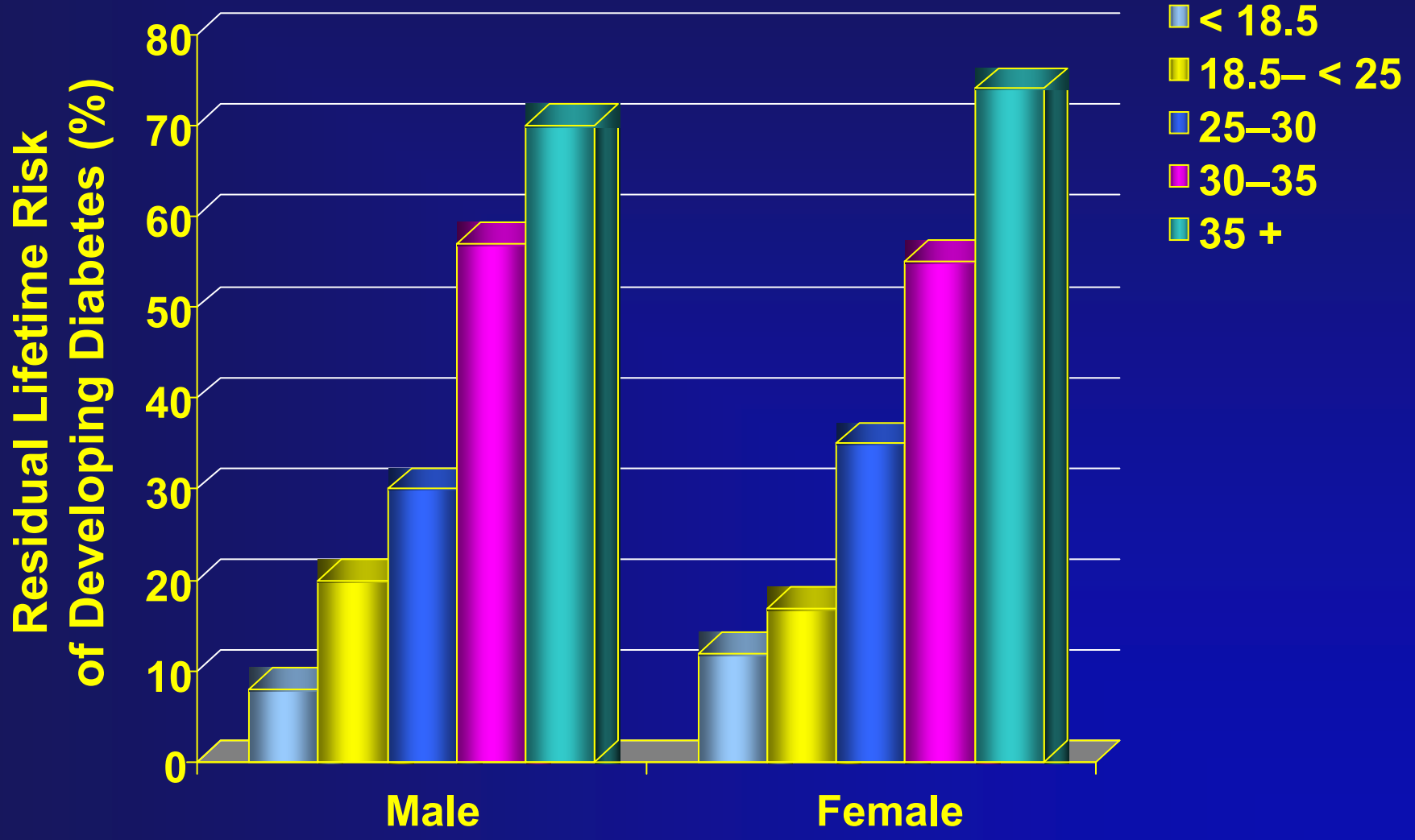


In populations with a high prevalence of T2DM, insulin resistance is well established long before the development of any impairment in glucose homeostasis.

Kahn SE *Diabetes* 1993

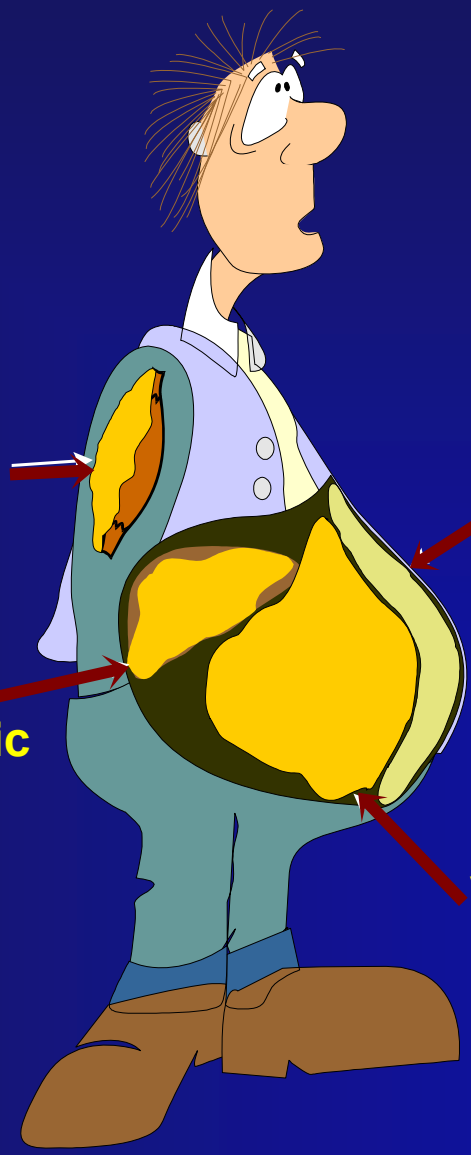
Pathogenesis of T2DM: role of diet

Increased BMI Leads to Increased Risk for Developing Diabetes in Both Genders

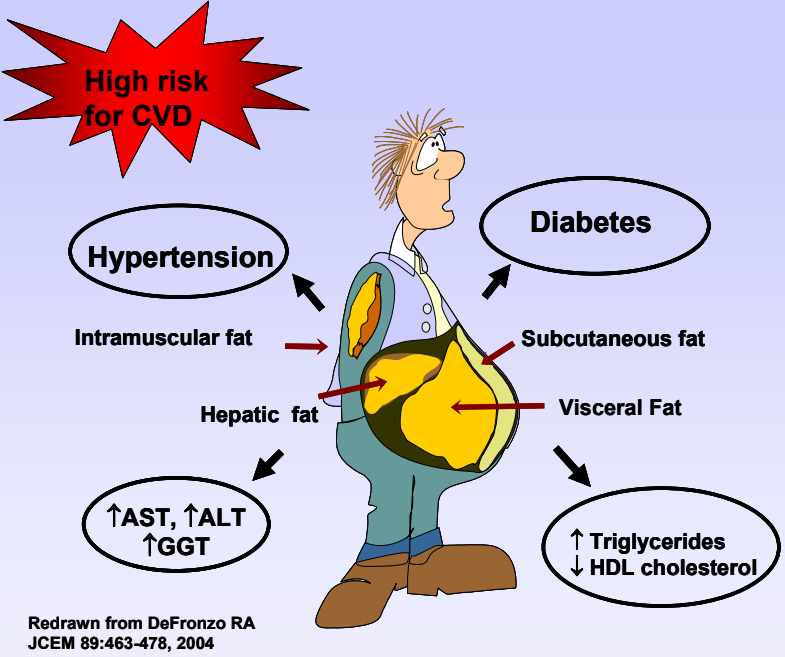


Narayan KM, et al. *Diabetes Care*. 2007;30:1562-1566.

Importance of fat distribution



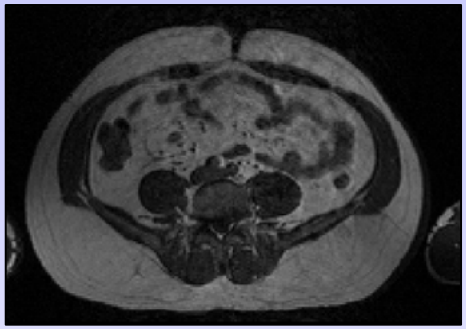
DeFronzo RA
JCEM 89:463-478, 2004



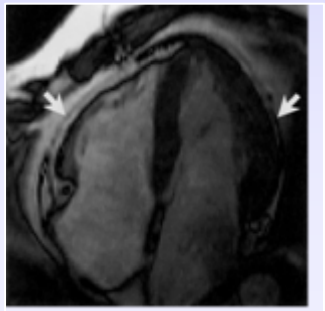
Redrawn from DeFronzo RA
JCEM 89:463-478, 2004

Magnetic Resonance for the quantification of body fat

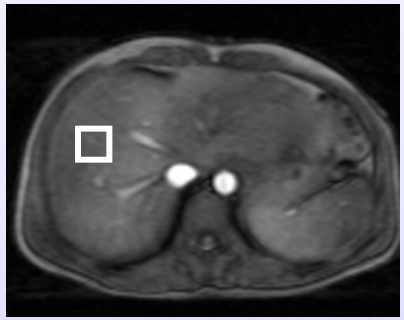
Visceral and subcutaneous fat



Abdominal fat

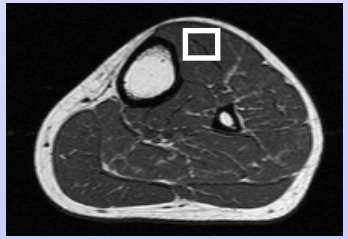


Cardiac fat



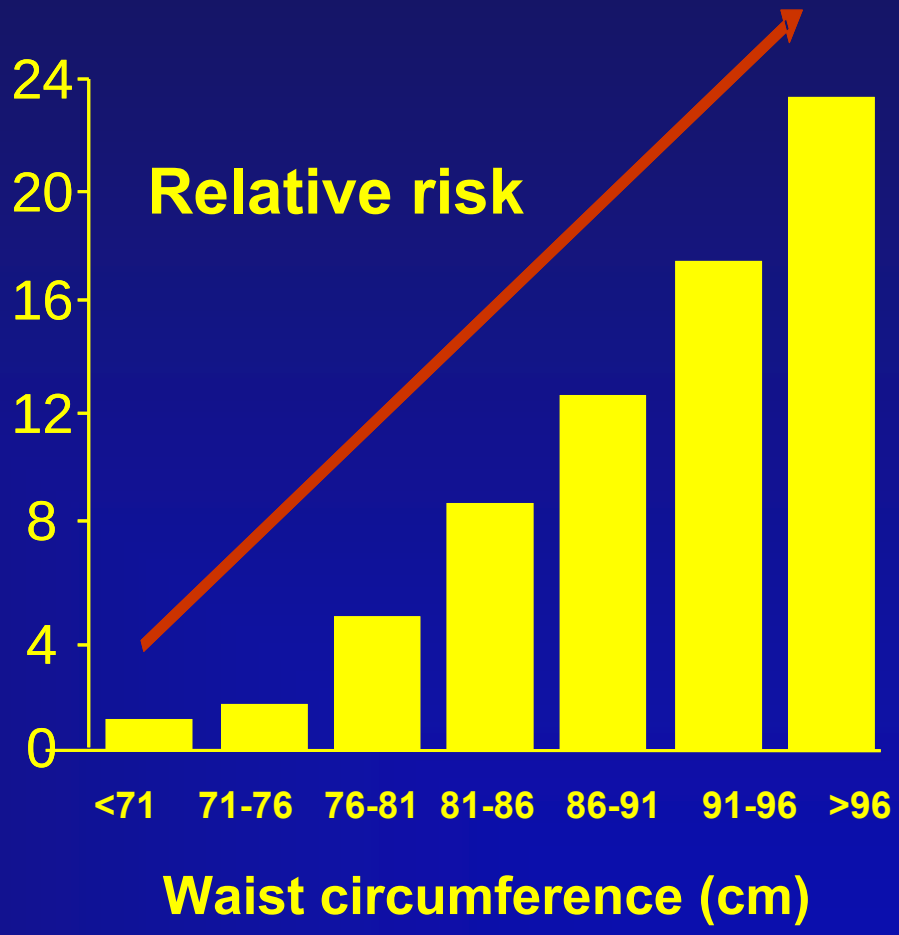
Liver fat

Muscle fat



Abdominal obesity increases the risk of developing type 2 diabetes

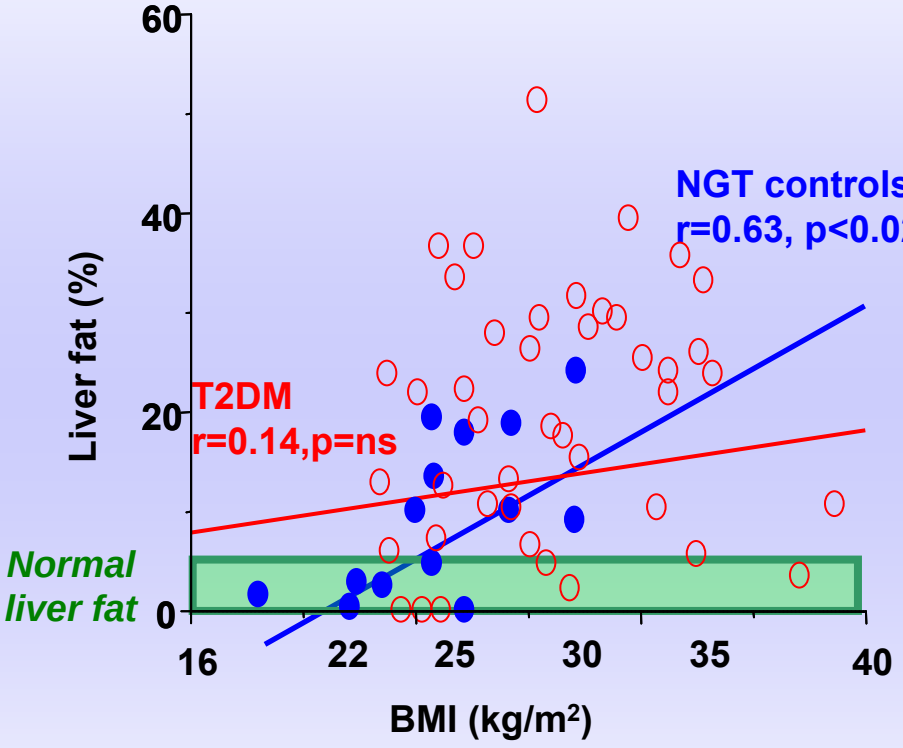
- Atherogenic Dyslipidemia
- Insulin Resistance
- Thrombotic State
- Inflammatory State

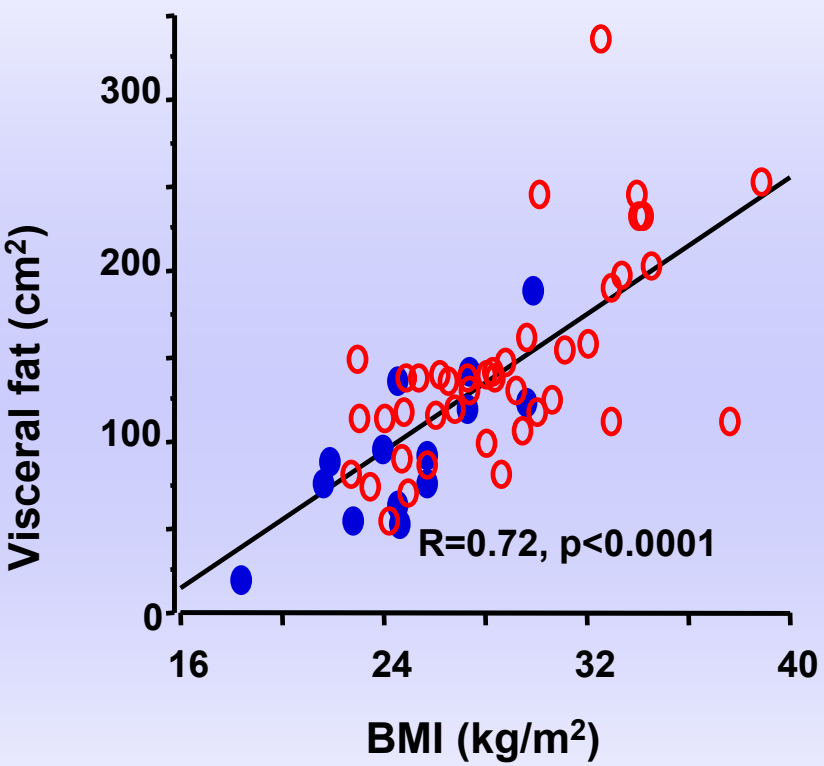


Adapted from *JAMA*. 2001;285:2486-2497; Alberti KG, et al. *Lancet*. 2005;366:1059-1062; Grundy SM, et al. *Circulation*. 2005;112:2735-2752.

Carey VJ *et al*, 1997

Visceral and hepatic fat in T2DM





● CT ○ T2D

Gastaldelli et al Gastroenterology 2007

Pathogenesis of Diabetes

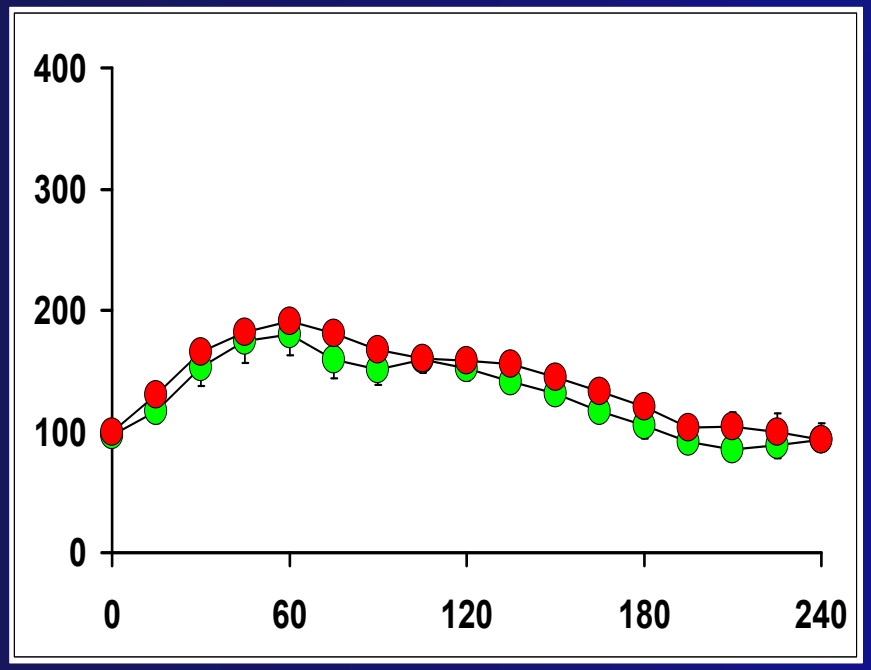
- Role of insulin resistance on
  - Fasting hyperglycemia
  - Postprandial hyperglycemia

Insulin Resistance

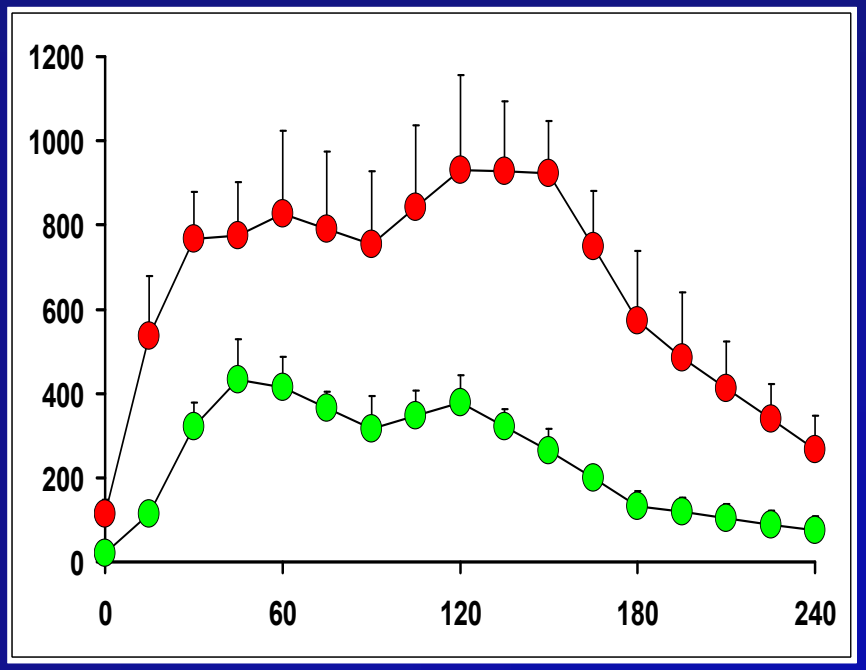
"a state (of a cell, tissue, system or body) in which greater-than-normal amounts of insulin are required to elicit a quantitatively normal response"

Berson & Yalow, 1970.

Glucose (mg/dl)



Insulin (pmol/l)



Healthy Control Obese

INSULIN-MEDIATED GLUCOSE UPTAKE IS REDUCED IN T2DM

Total Body Glucose Uptake (mg/kg•min)

7
6
5
4
3
2
1
0

CON

T2DM

Controls

Diabetics

p<0.01
p<0.05

12
8
4
0

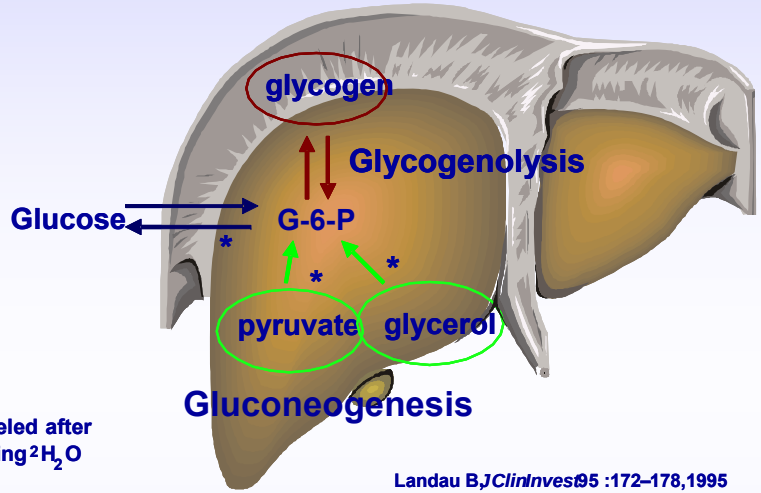
Leg Glucose Uptake (mg/kg leg wt per min)

0 40 60 100 140 180

Time (Minutes)

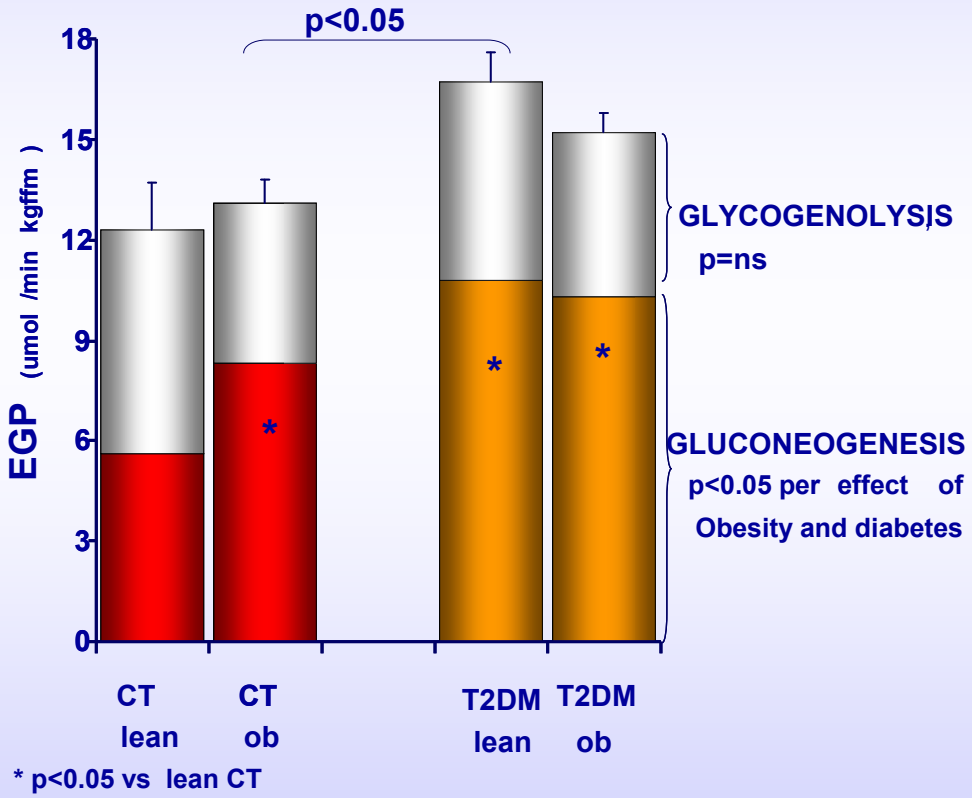
DeFronzo et al, JCI 63:939-46, 1979; JCI 76:149-55, 1985

Hepatic glucose production =Gluconeogenesis+Glycogenolisis



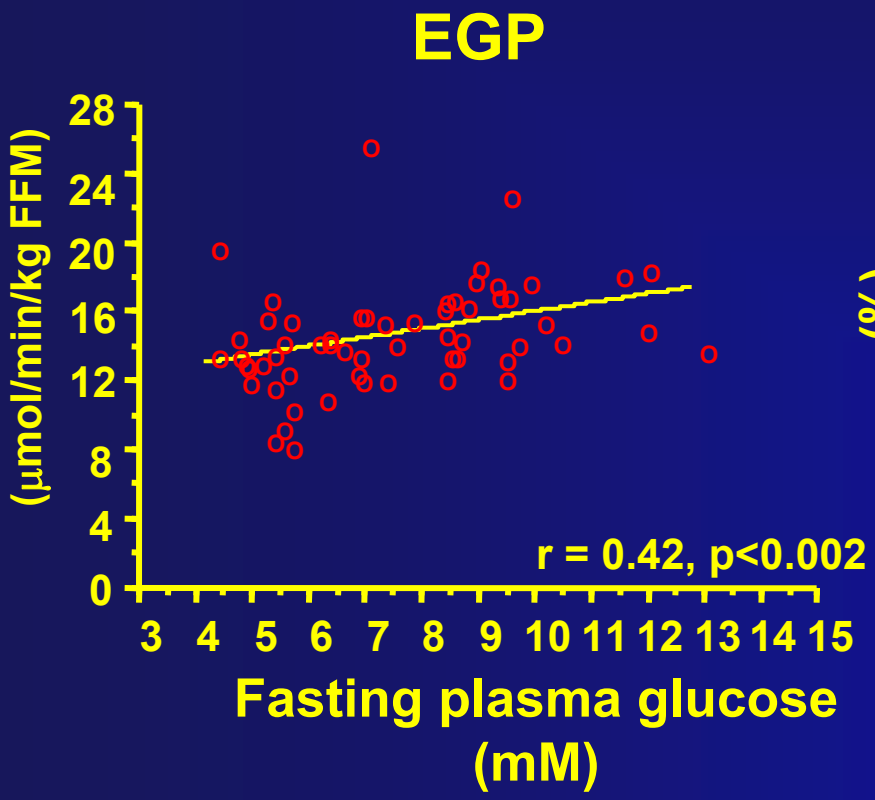
* Labeled after drinking ^2H_2O

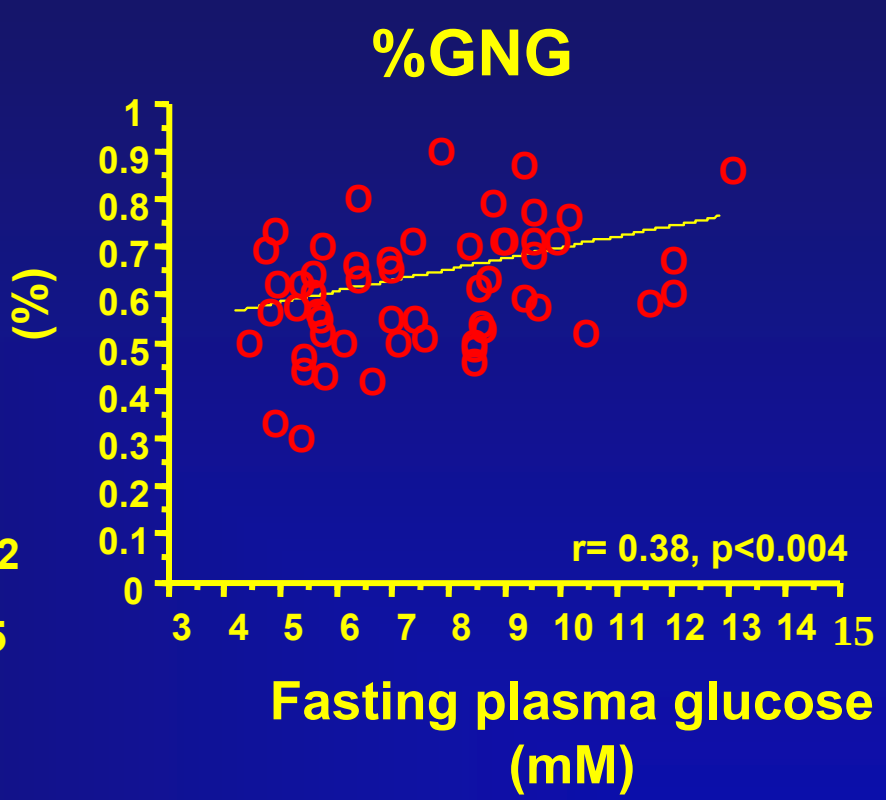
Landau B,*J Clin Invest* 95 :172–178,1995



Gastaldelli A *et al*, ***Diabetes*** Aug; 49 (8): 1367-73, 2000

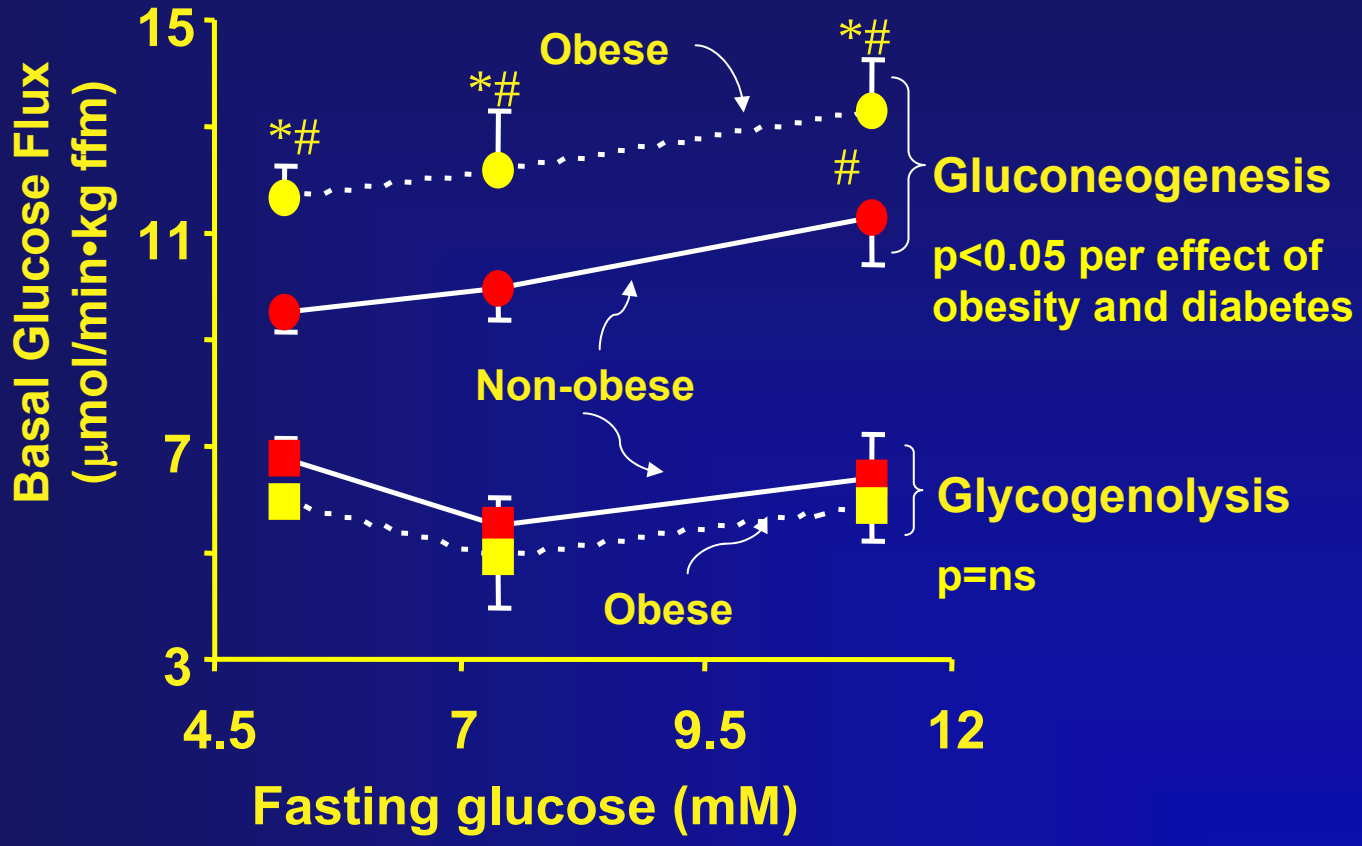
Fasting plasma glucose concentration is increased proportionally to % GNG and EGP





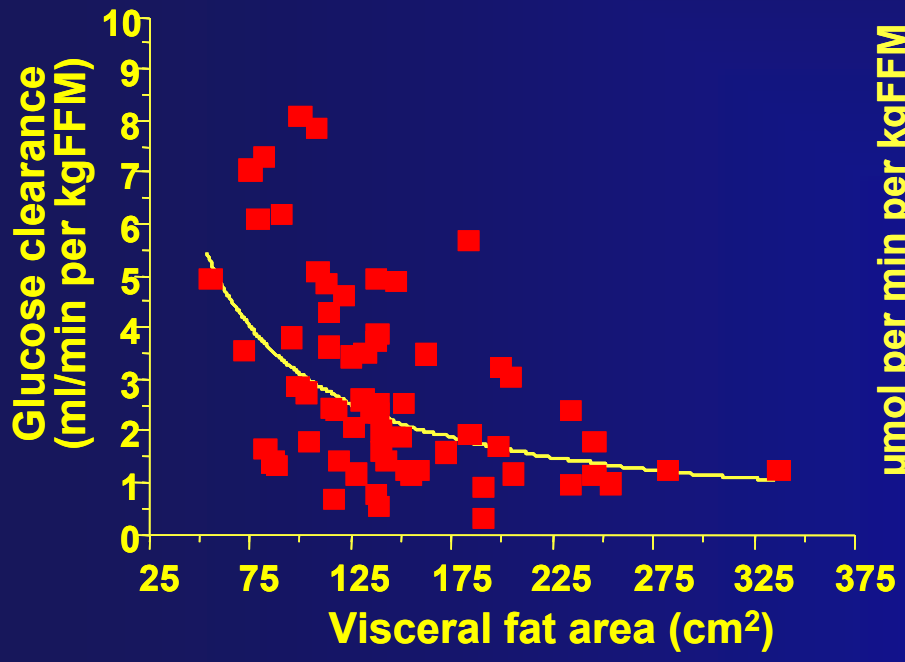
Gastaldelli A et al *J Clin Endocrinol Metab* 89:3914-3921, 2004

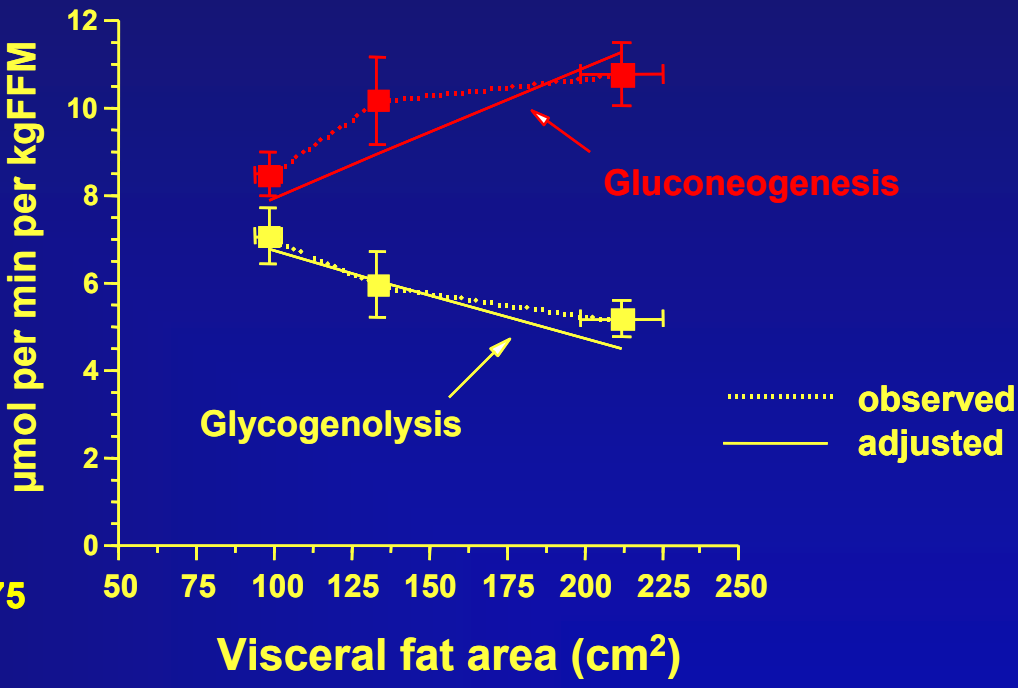
Components of fasting glucose production in CT e T2DM subjects stratified by FPG and obesity



Gastaldelli A et al *J Clin Endocrinol Metab* 89:3914-3921, 2004

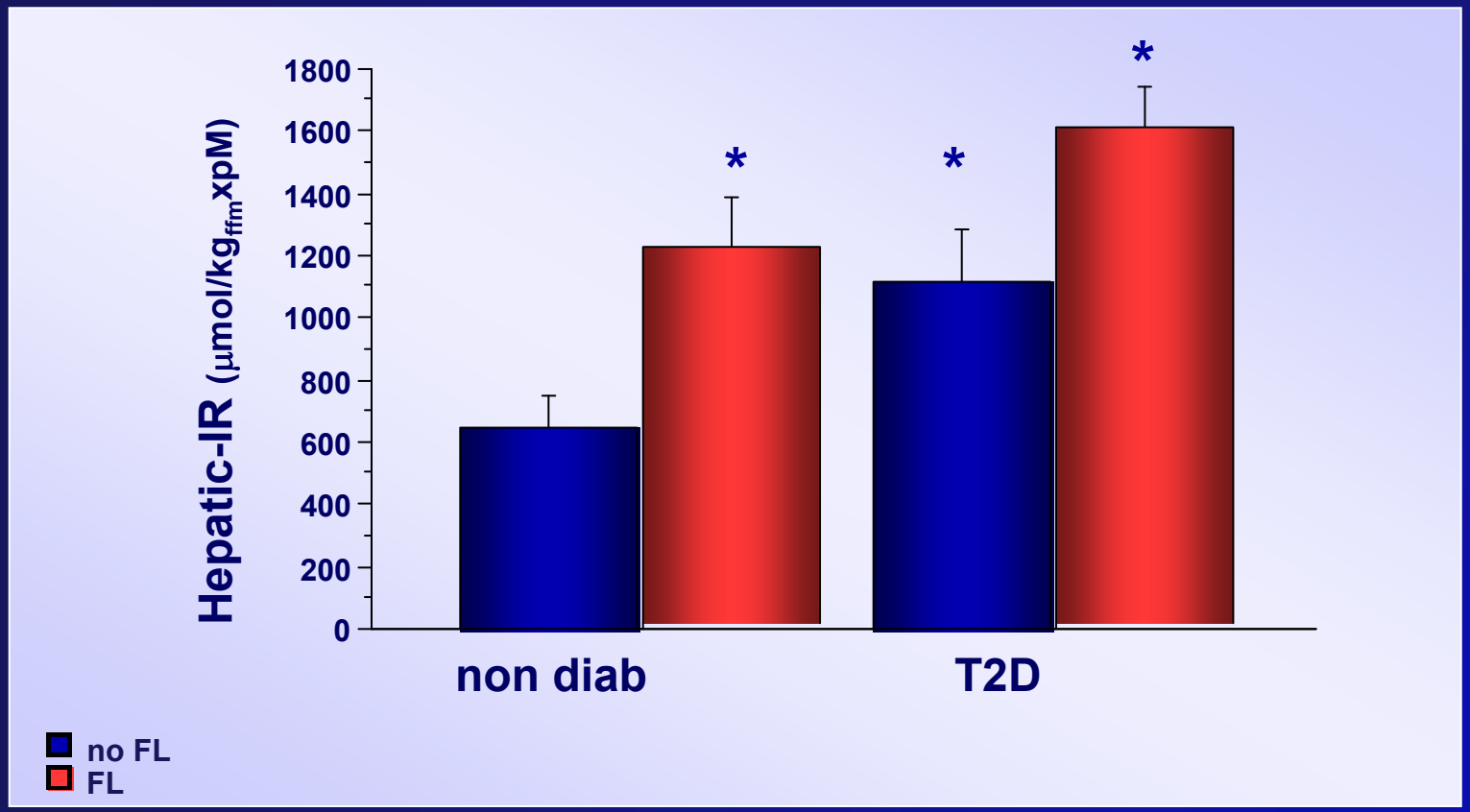
Effect of visceral fat accumulation on glucose clearance and glucose production in T2DM subjects





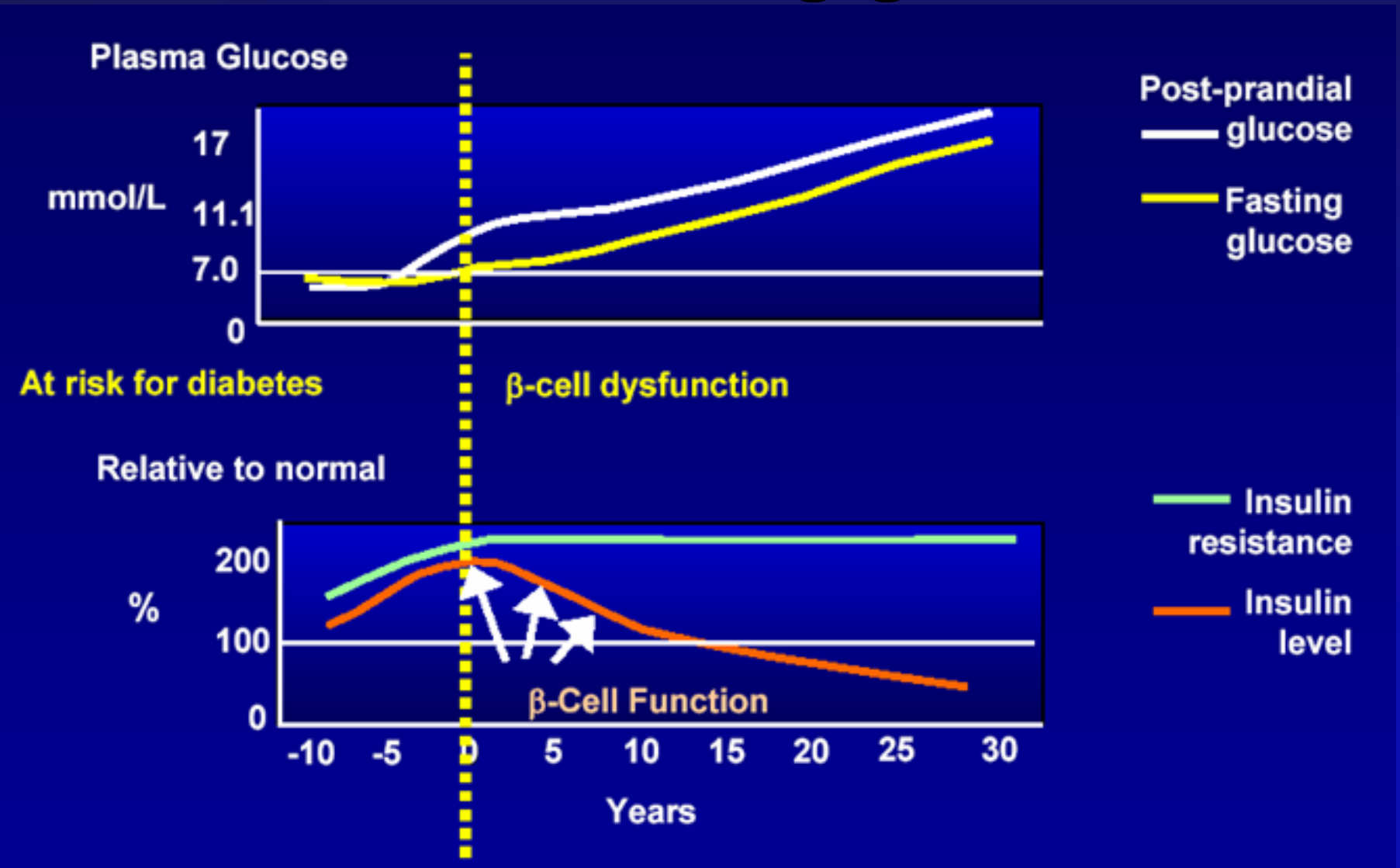
Gastaldelli et al J Clin End Metab 87, 2002

Fasting hepatic insulin resistance in T2DM with fatty liver disease

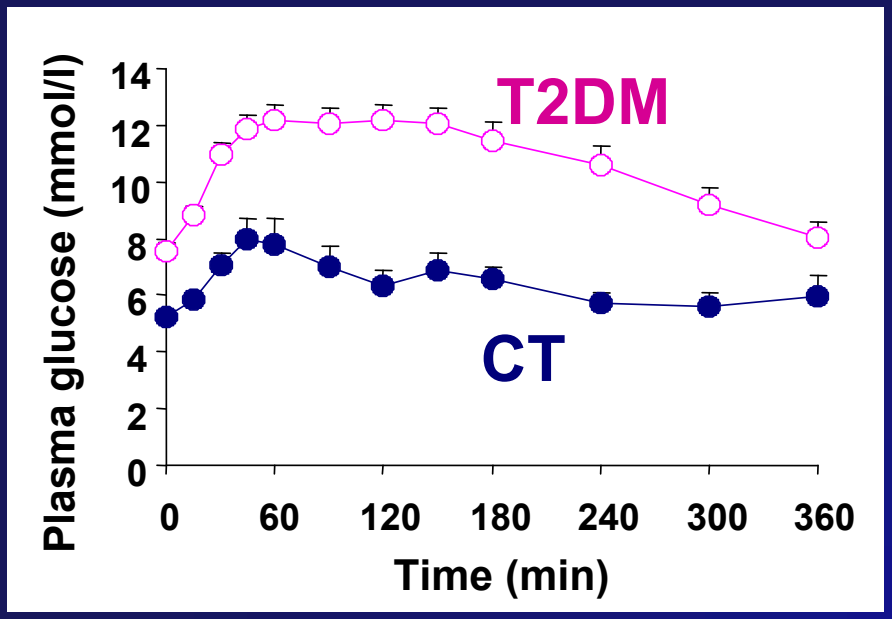


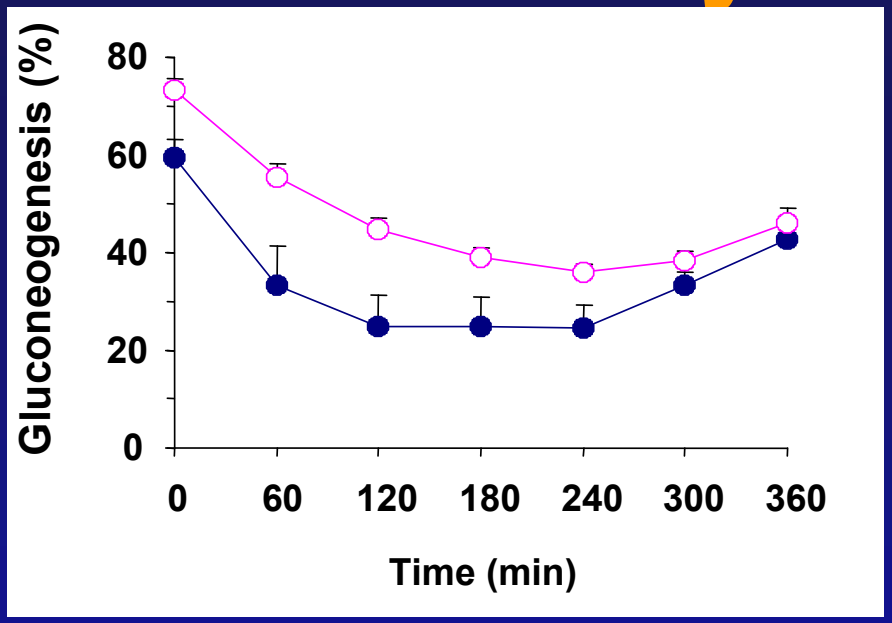
Gastaldelli et al Gastroenterology 2007

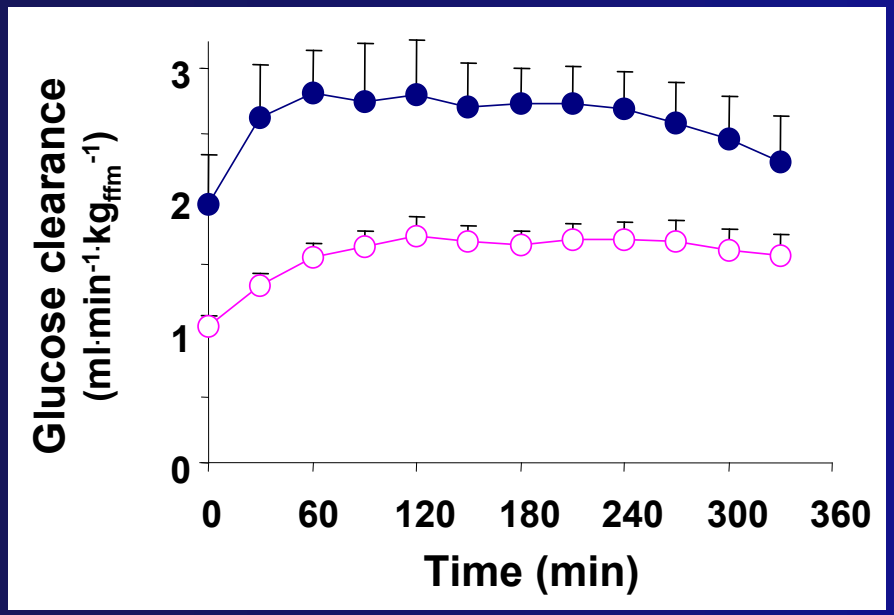
Postprandial glucose deteriorates before fasting glucose.

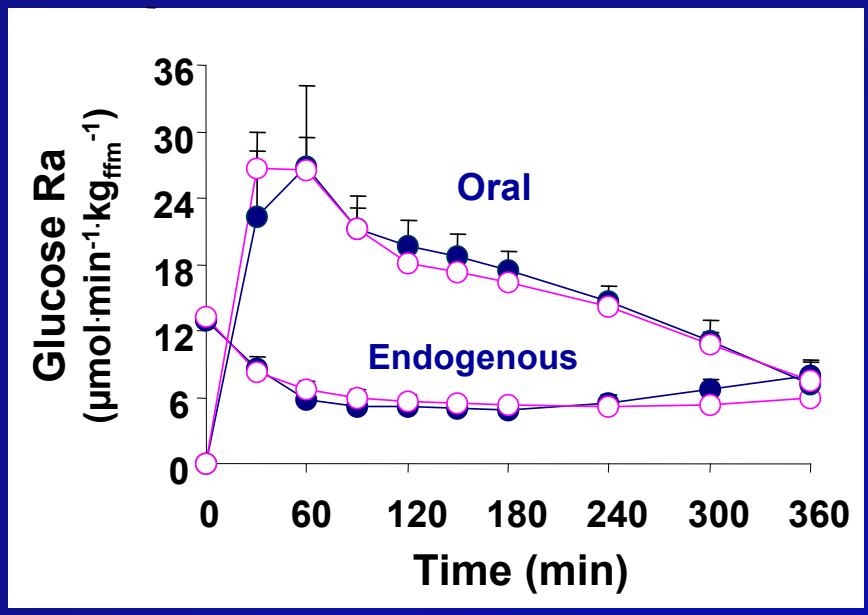


Mixed meal insulin sensitivity









Gastaldelli et al Clin Pharm Therap 2007

High fat diet

Obesity

Visceral Obesity

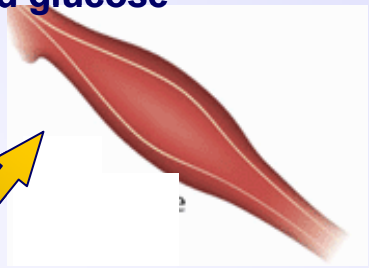
Insulin resistance

↑FFA

Decreased insulinc clearance
Increased Hepatic IR,
GNG and VLDL secretion

Increased lipolysis

Decreased glucose uptake



↑VLDL

GLUCOSE

↑ROS

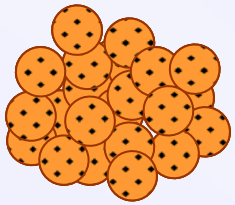
↑β-oxidation

↑GNG precursors

↑FFA

↑DNL

↑TG



FFA

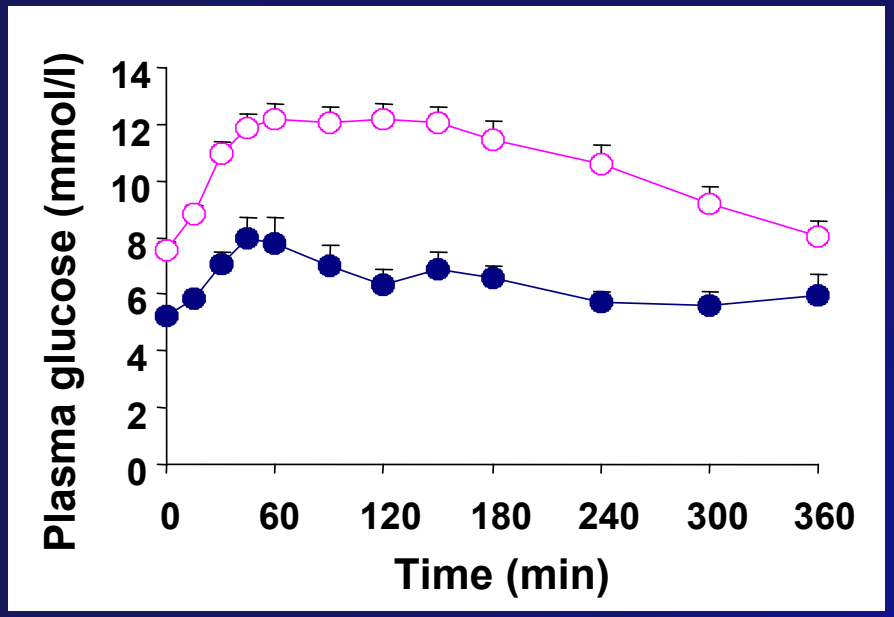
↑FFA, glycerol,
GNG precursor
↓Adiponectin
↑Insulin

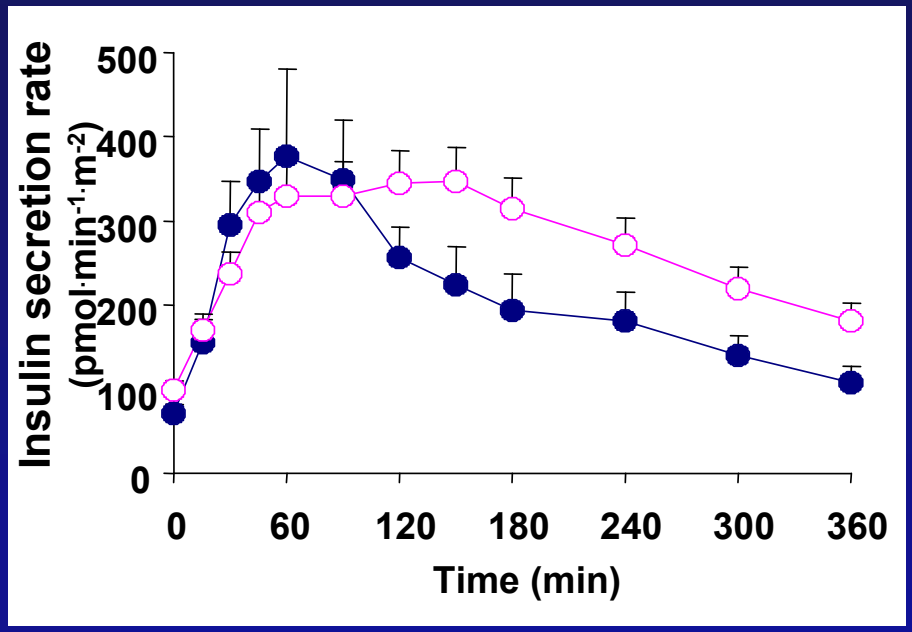
↑INSULIN

Pathogenesis of Diabetes

- Role of insulin resistance
- Role of insulin secretion/beta cell

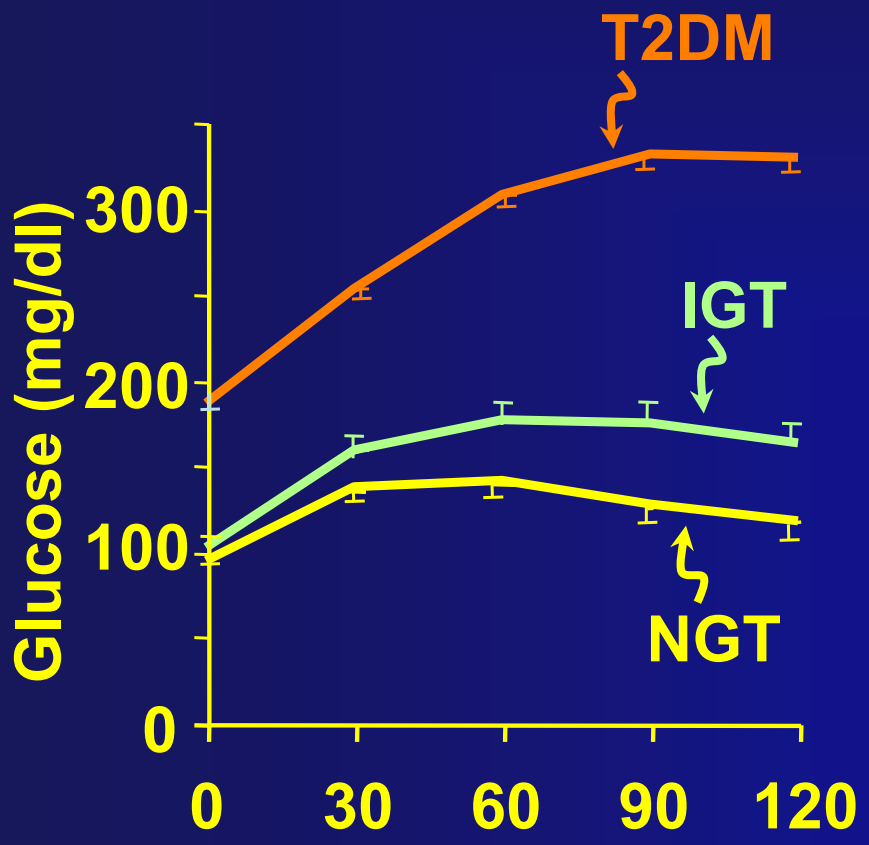
Mixed meal insulin secretion

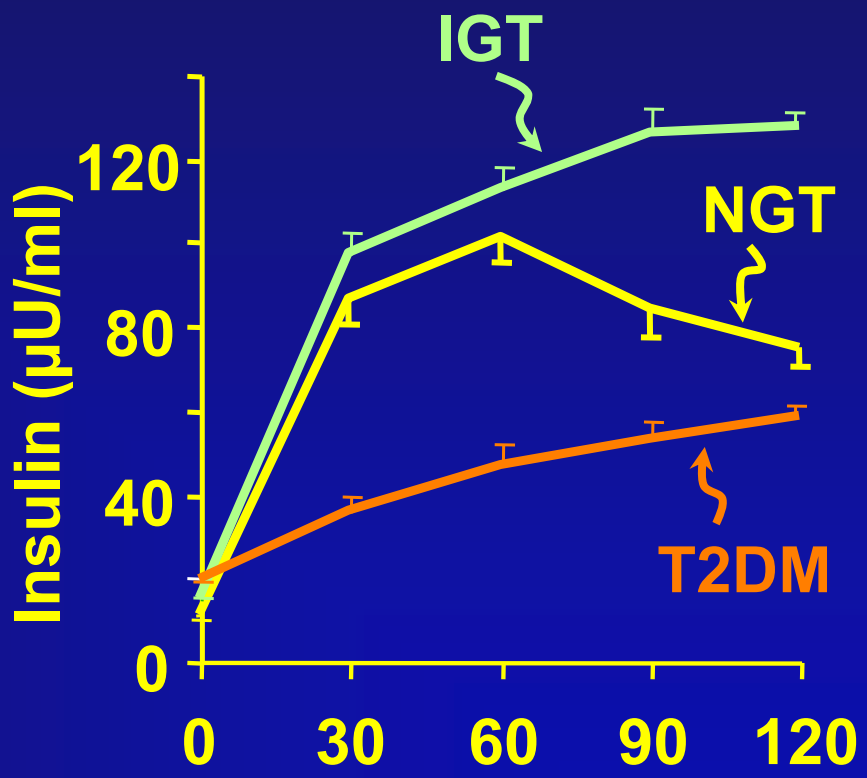




Gastaldelli et al Clin Pharm Therap 2007

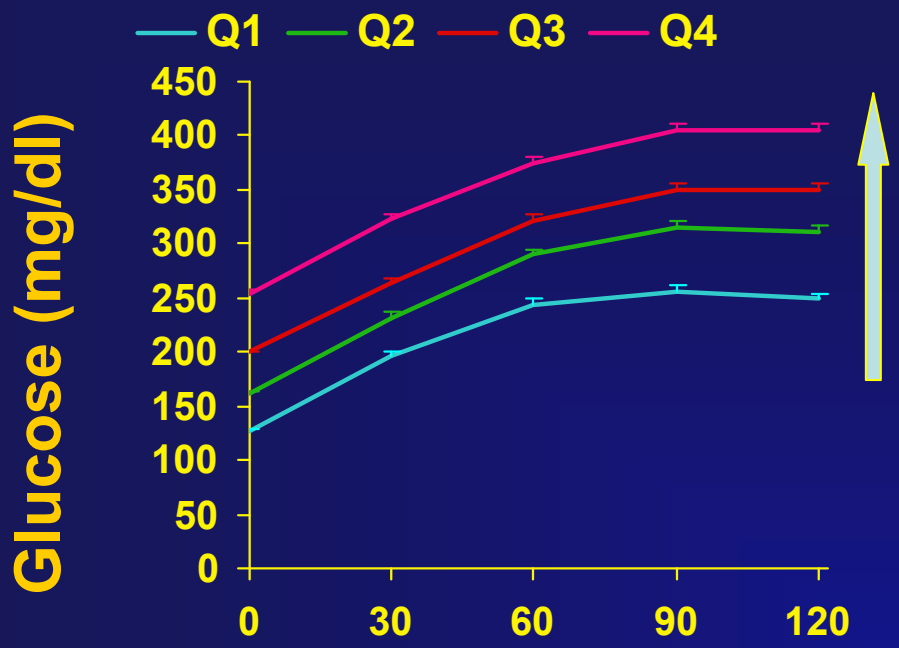
PLASMA GLUCOSE and INSULIN RESPONSE DURING OGTT

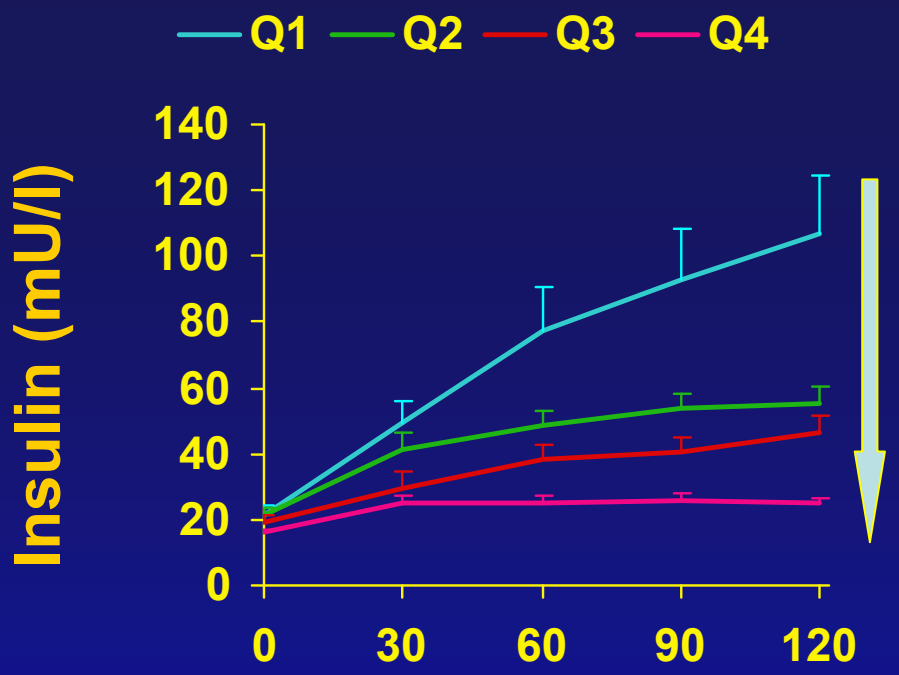


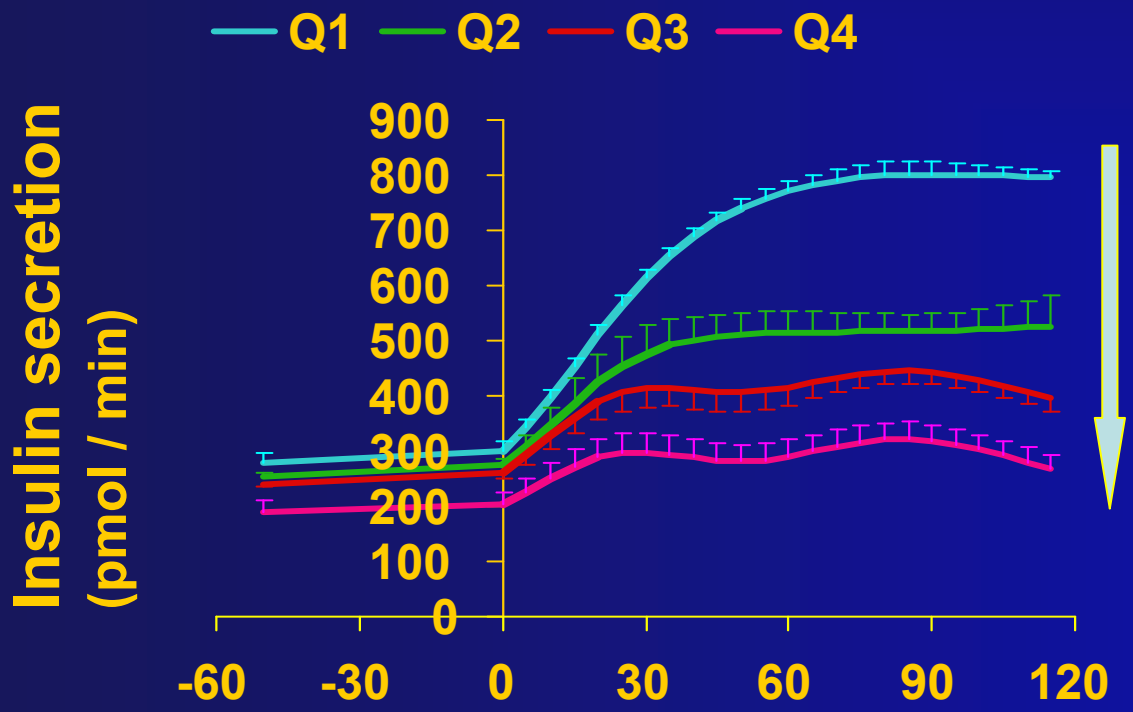


TIME (minutes)

Gastaldelli et al *Diabetologia* 2004







Q1 FPG<146mg/dl

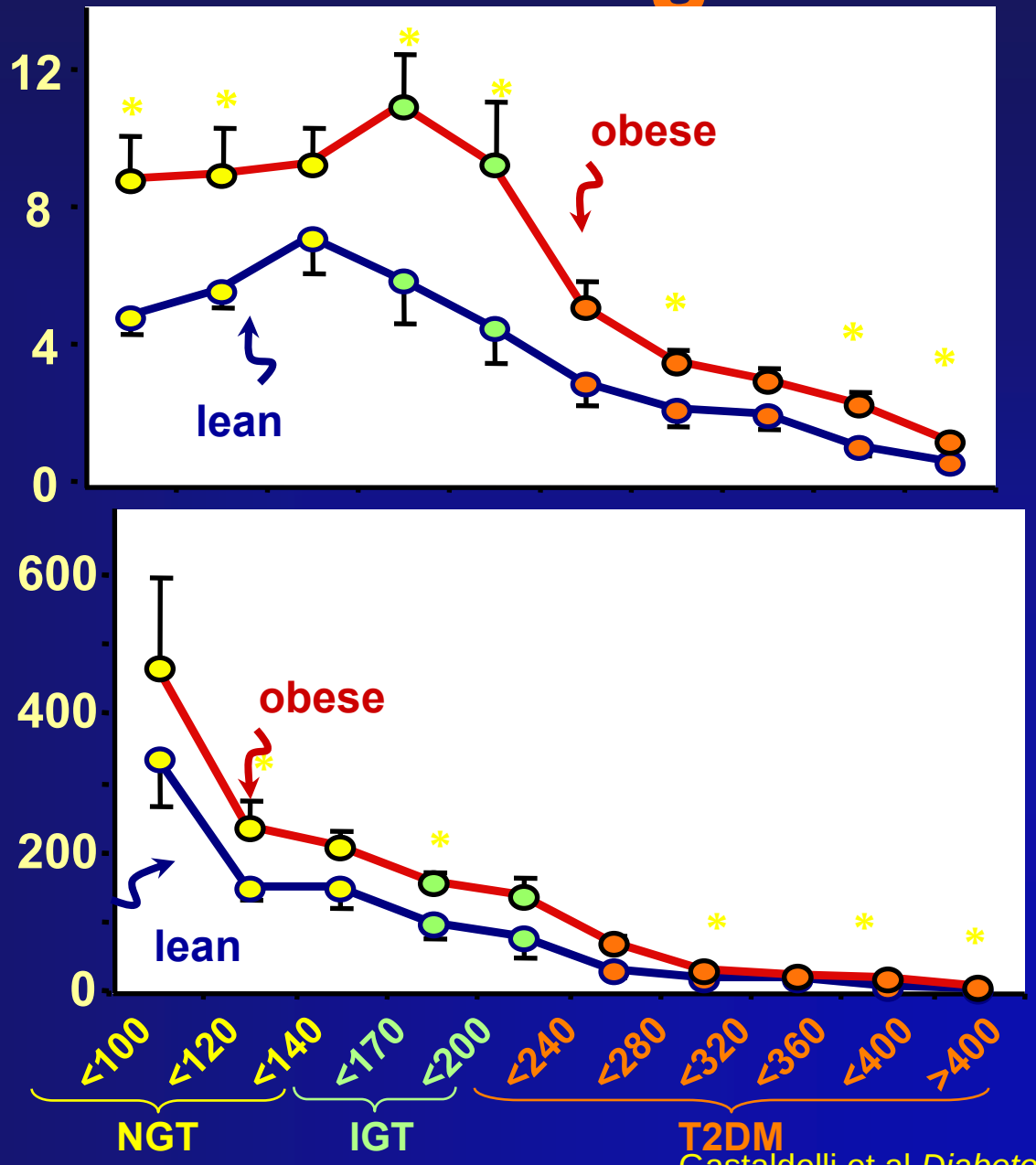
Q2 FPG<178mg/dl

Q3 FPG<225mg/dl

Q4 FPG>225mg/dl

Gastaldelli et al *Diabetologia* 2004

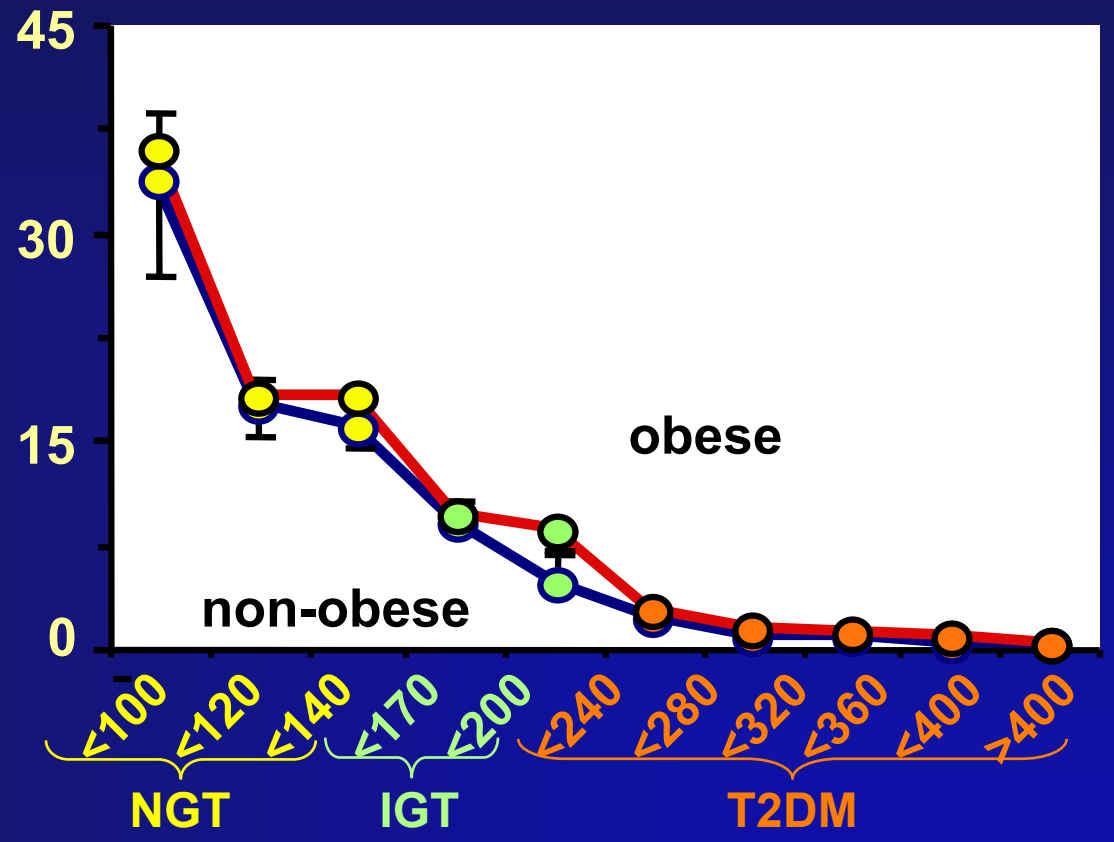
β-cell function during OGTT



Gastaldelli et al *Diabetologia* 2004

Ins Secretion ÷ Ins Resistance index

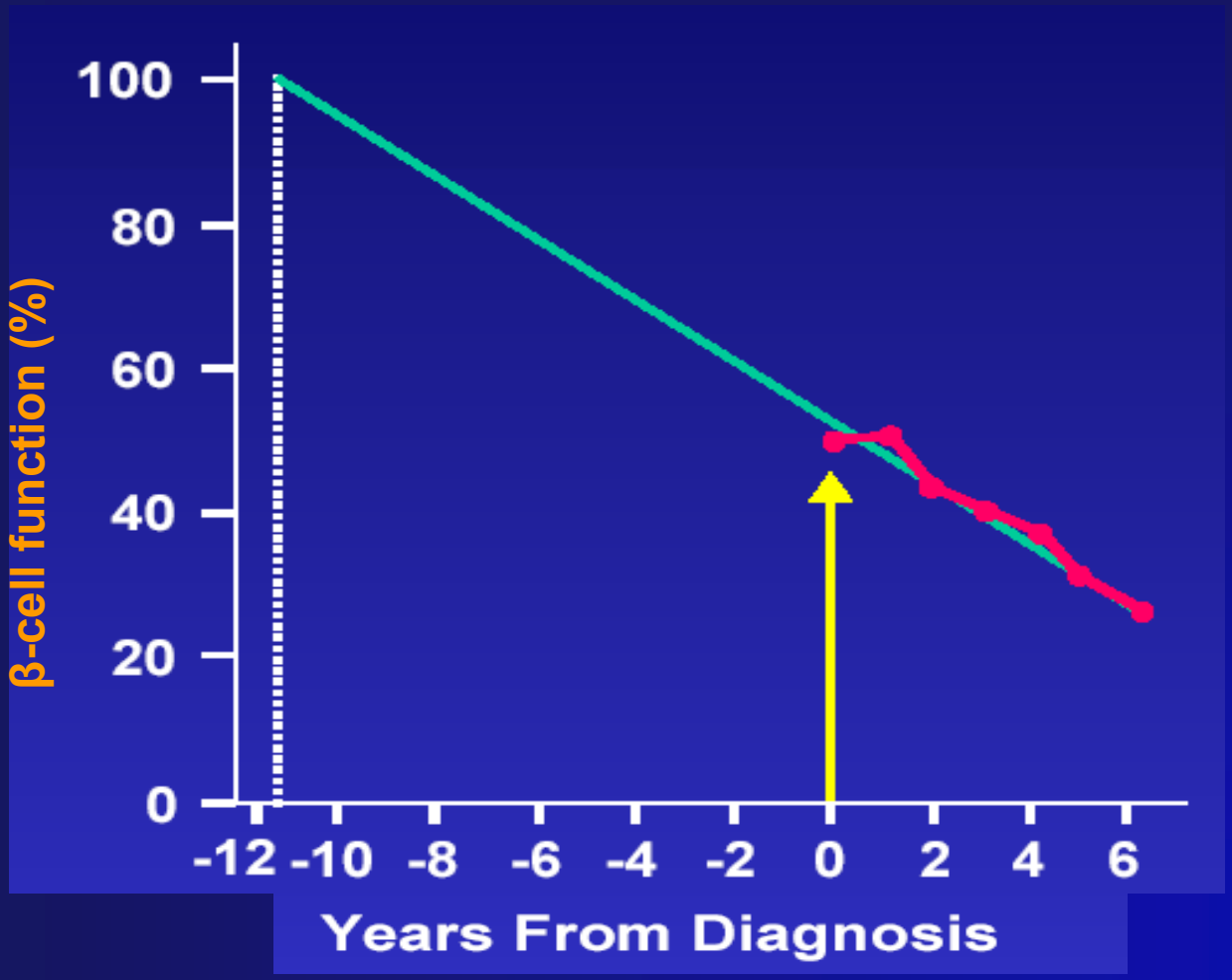
$\Delta I/\Delta G \div IR$
$(ml/min \cdot kg_{FFM})$
0-120 min



At the stage of IGT, individuals have lost over 80% of their beta cell function

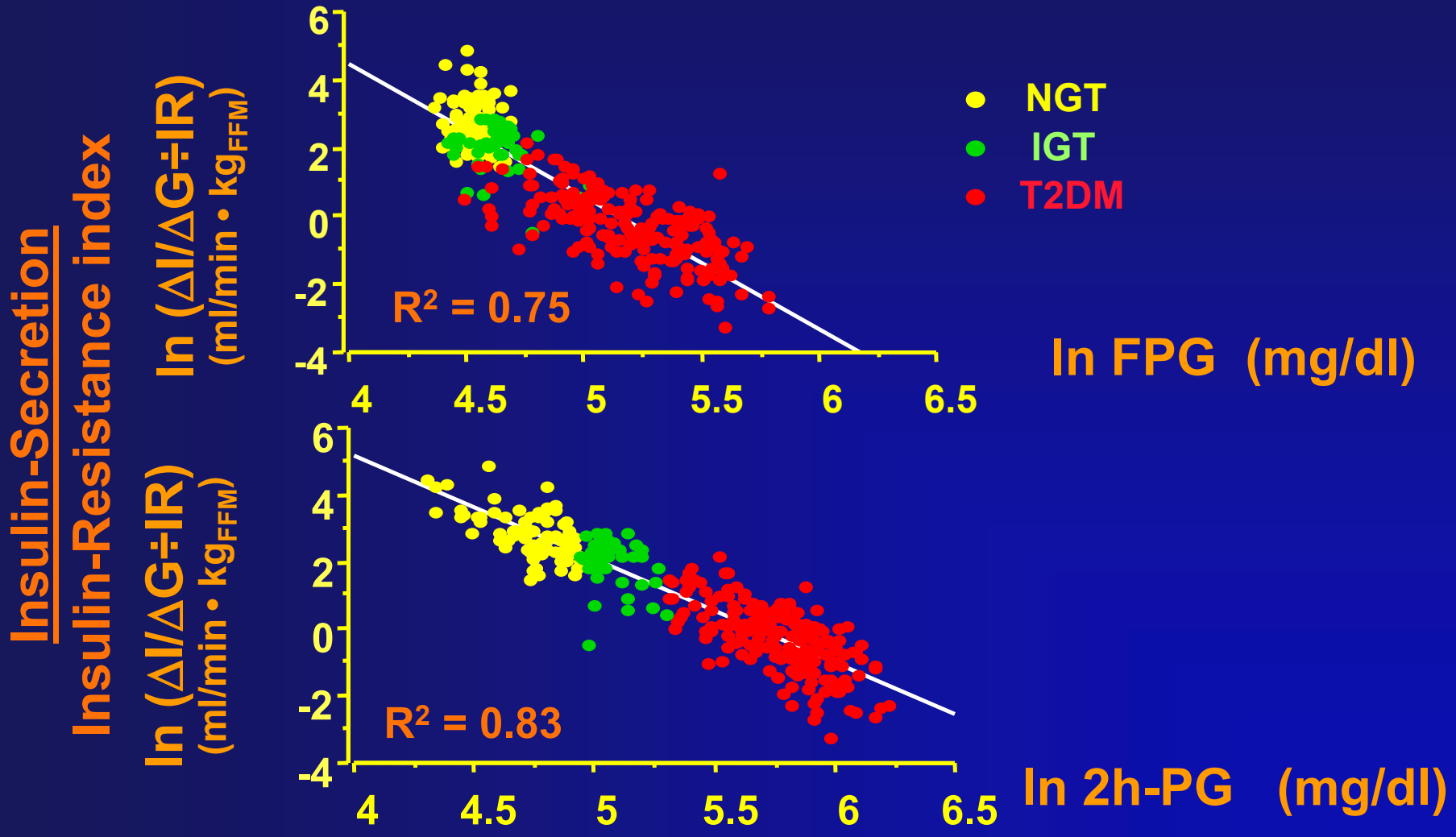
Gastaldelli et al *Diabetologia* 2004

β-cell function in the UKPDS



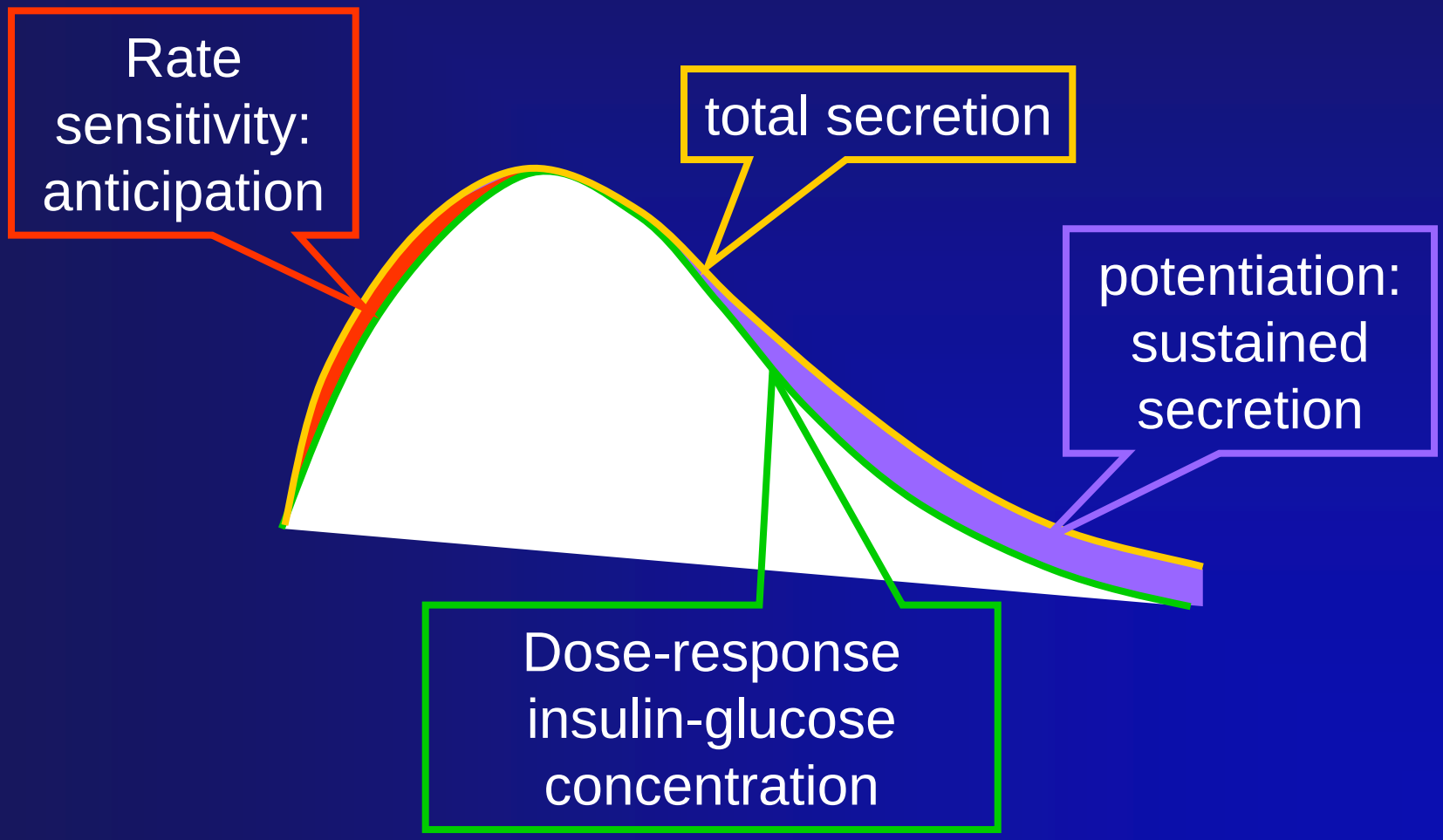
Holman RR *Diabetes Res Clin Pract* 1998

Log normalization of the relationship between the Insulin-Secretion/Insulin-Resistance index and plasma glucose

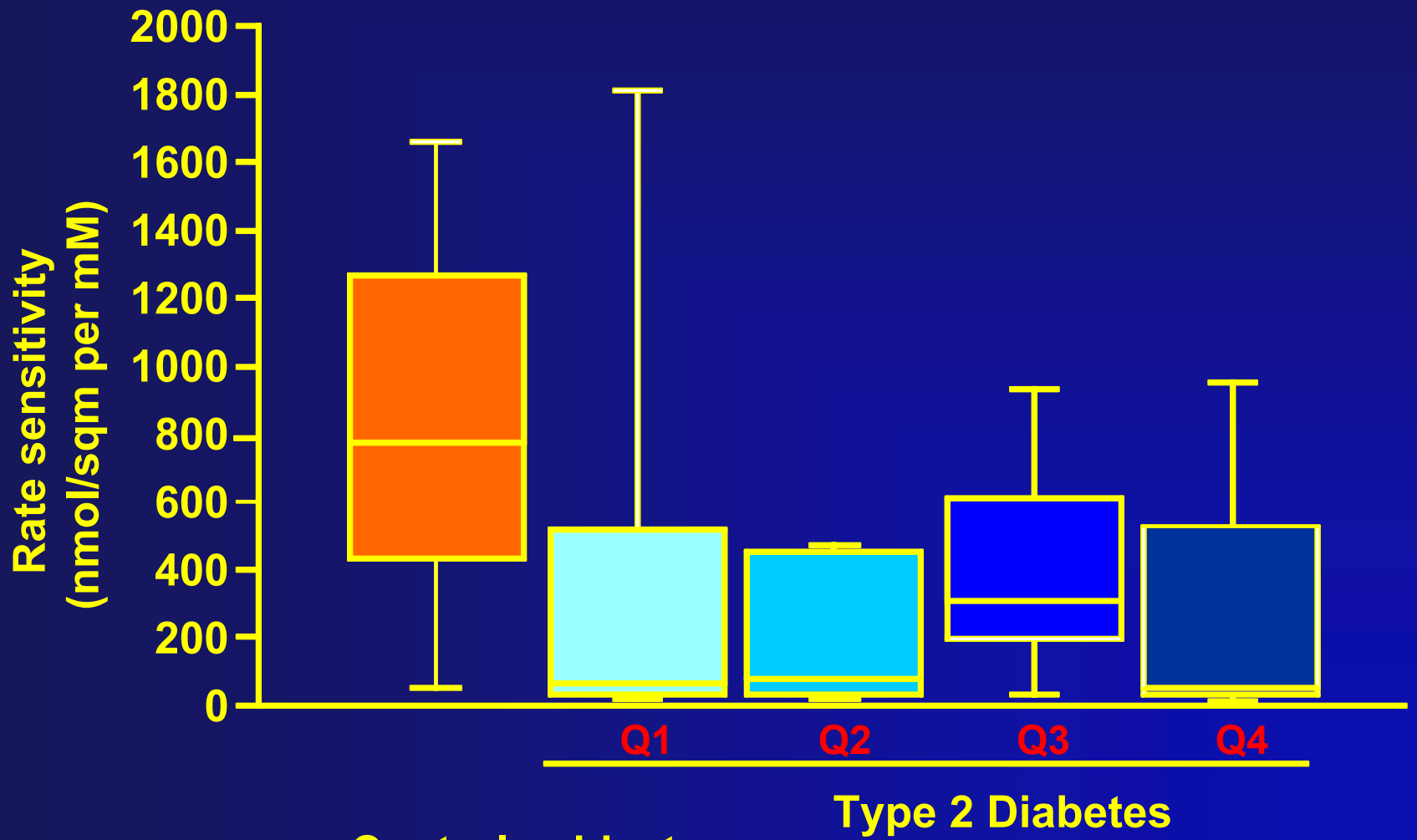


Gastaldelli et al *Diabetologia* 2004

β-cell model: insulin secretion characteristics in response to a meal

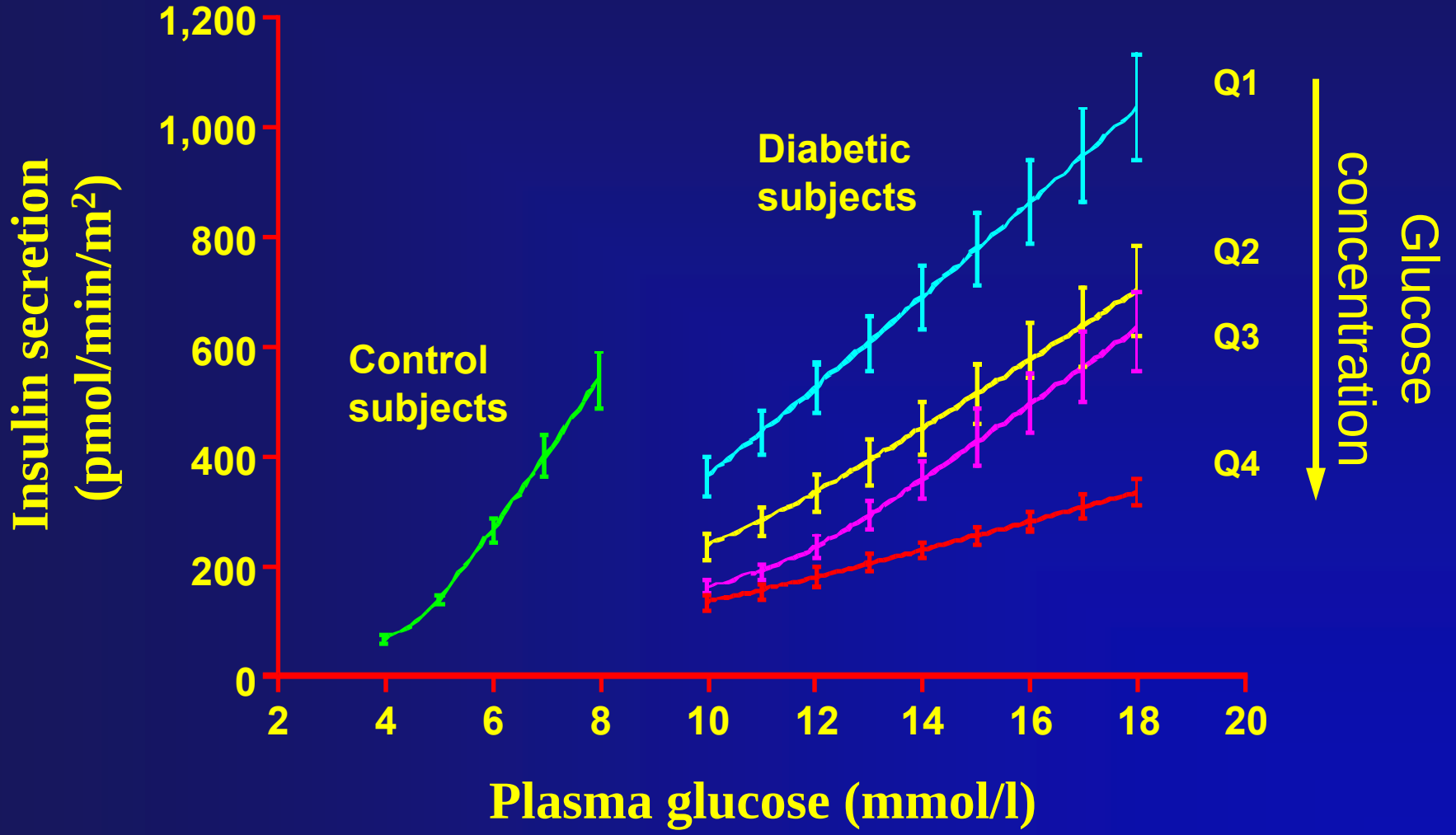


Rate sensitivity by quartile of fasting hyperglycemia

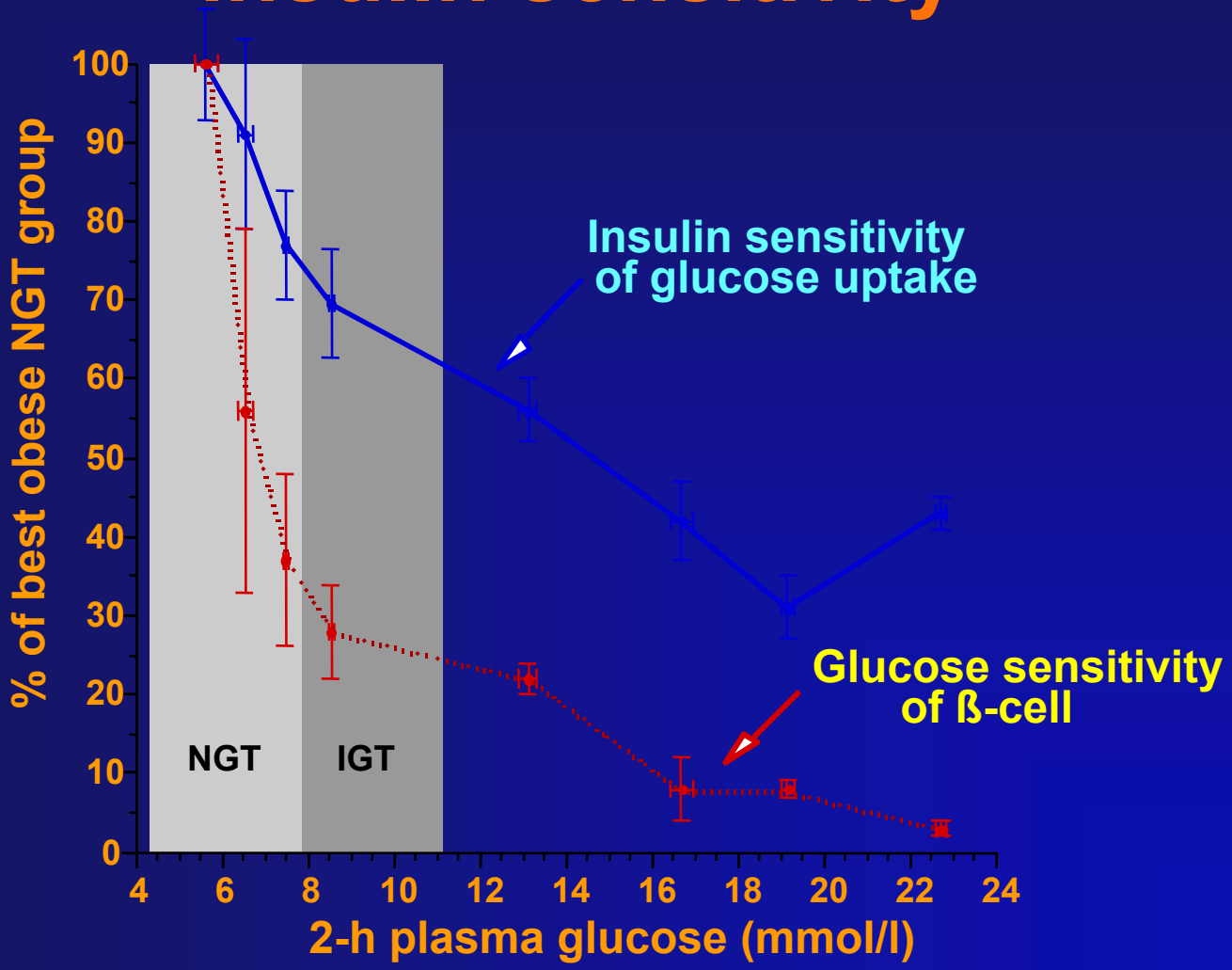


Ferrannini, Gastaldelli et al JCEM 2004

Dose-response for glucose-stimulated insulin secretion by quartile of fasting hyperglycemia



glucose sensitivity and insulin sensitivity

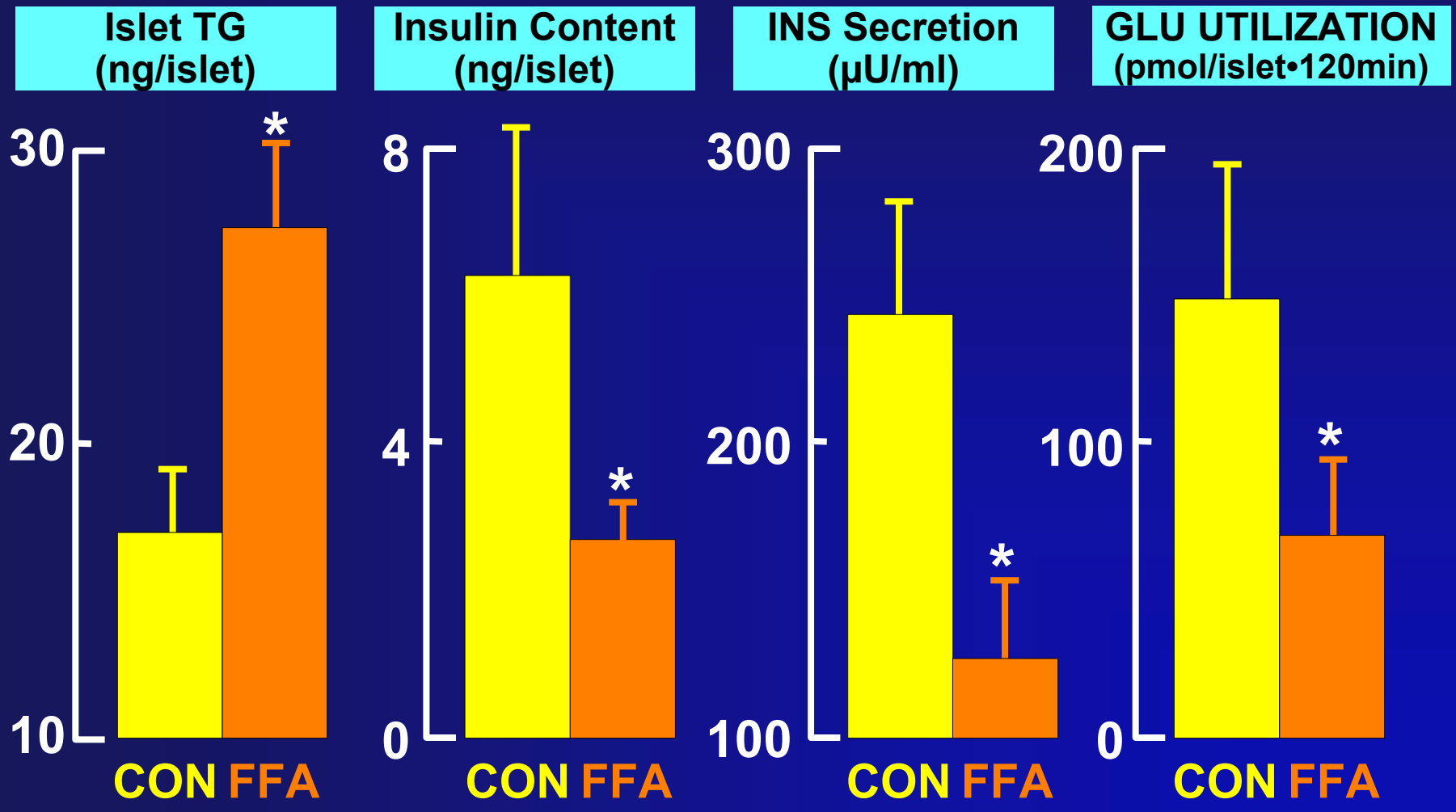


Ferrannini, Gastaldelli et al JCEM 2004

FFA AND INSULIN SECRETION

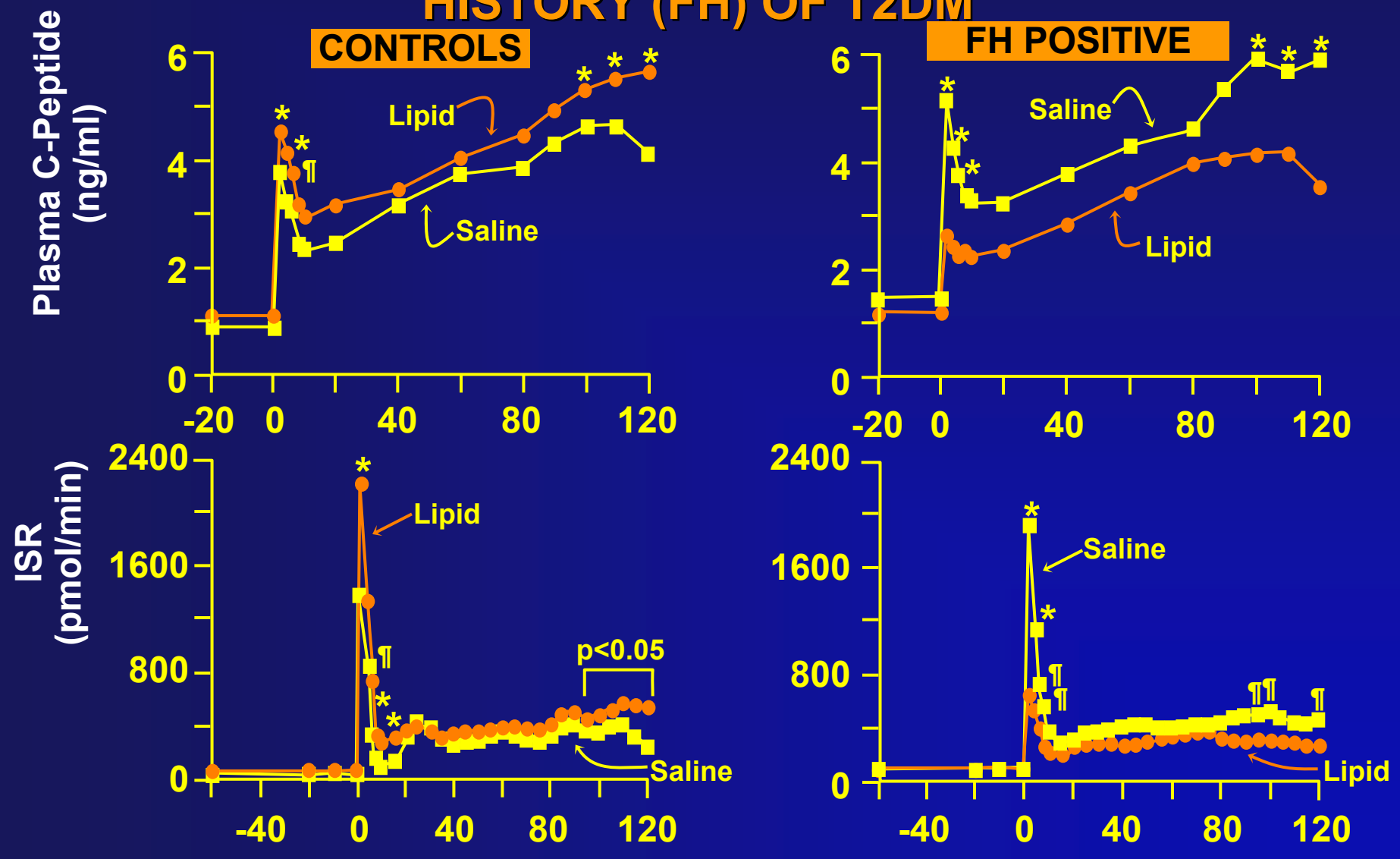
- In humans, increased plasma FFA levels enhance basal and glucose-stimulated insulin secretion after 2-4 h and 24 h of lipid infusion
- In rats,
  - increased plasma FFA levels in vivo and in vitro acutely (3-6 h) stimulate basal and glucose stimulated insulin secretion;
  - after 48 h, the insulin stimulatory effect of FFA is lost
  - islet triglyceride accumulation precedes deterioration of insulin secretion and overt diabetes

EFFECT OF INCUBATION (48 HOURS) OF HUMAN ISLETS WITH FREE FATTY ACIDS (OLEATE + PALMITATE)



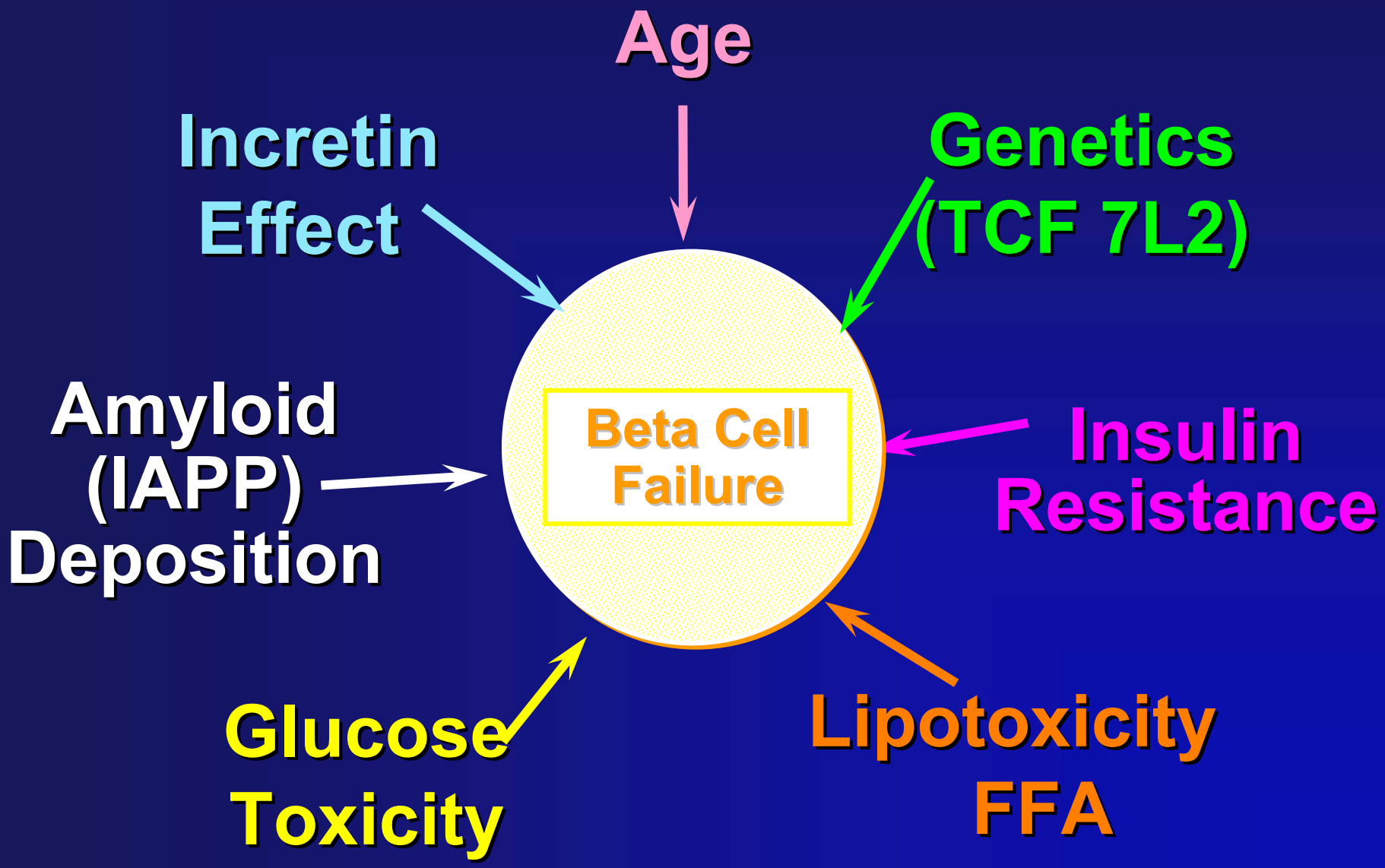
Lupi, *Diabetes* 51:1437, 2002

EFFECT OF LIPID INFUSION (48 HOURS) ON PLASMA C-PEPTIDE RESPONSE AND INSULIN SECRETORY RATE (ISR) IN SUBJECTS WITH AND WITHOUT A STRONG FAMILY HISTORY (FH) OF T2DM



Kashyap, Gastaldelli, et al *Diabetes* 52:2461, 2003

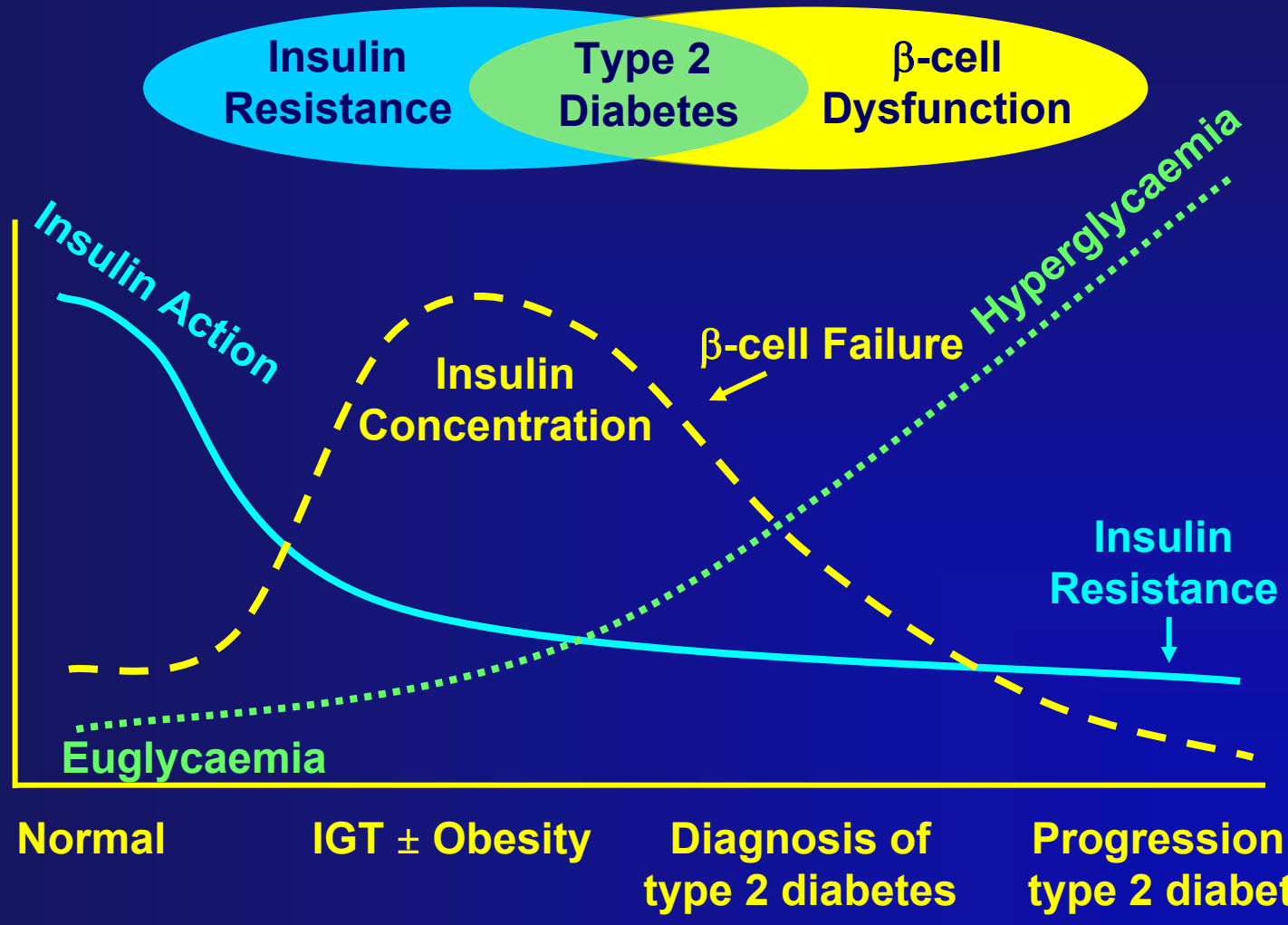
Etiology of β–cell failure in T2DM



Summary

- Glucose intolerance and T2DM depend on hepatic and peripheral insulin resistance and impaired beta cell function
- At the stage of IGT, individuals have lost over 80% of their beta cell function

Dual defect of type 2 diabetes: treating a moving target



DeFronzo et al. Diabetes Care 1992;15:318-68

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