Epidemiology and Pathophysiology of Type 2 Diabetes and Obesity

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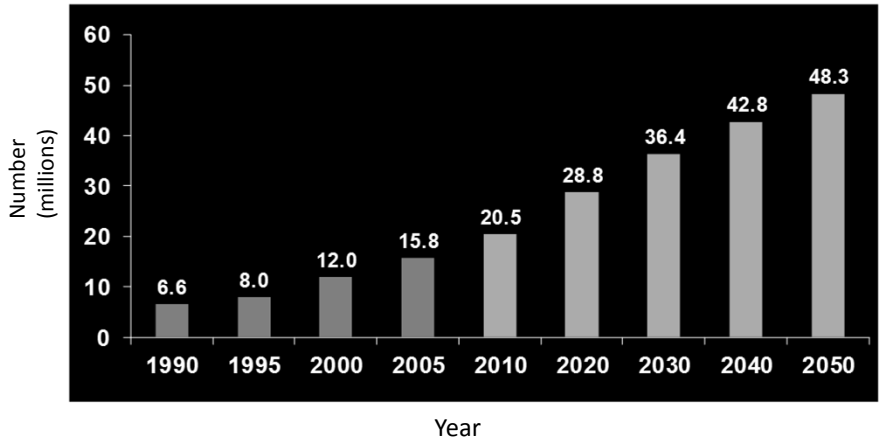
Diabetes in the USA

- **>26 million Americans with diabetes in 2011**
- **About 10% have type 1 diabetes**
- **Many more with either IGT, IFG or both**
- **Many Americans today with the metabolic syndrome at risk for diabetes**

The epidemic continues…

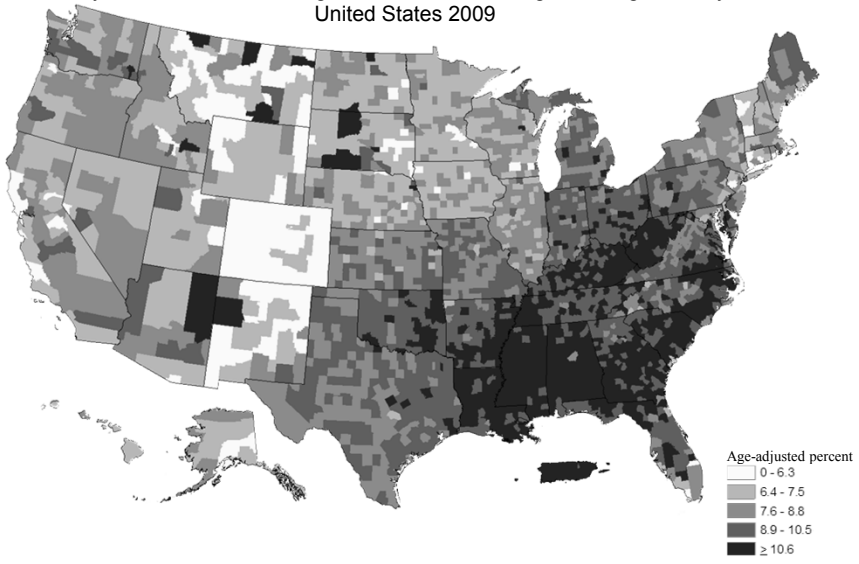
CDC 2008; National Diabetes Fact Sheet and the National Diabetes Surveillance System; http://apps.nccd.cdc.gov/DDTSTRS/default.aspx

Actual and Projected Diagnosed Diabetes in the United States, 1990-2050



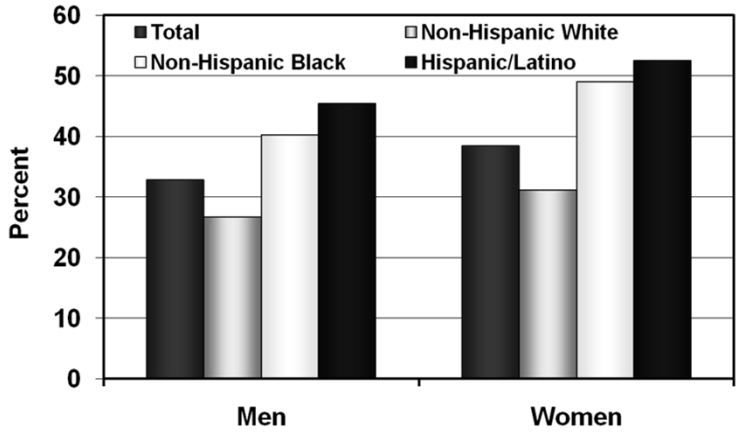
National Diabetes Surveillance System. Available at: http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm.
Narayan KMV, et al. *Diabetes Care*. 2006;29:2114-2116.

County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2009



www.cdc.gov/diabetes

Estimated lifetime risk of developing diabetes for individuals born in the United States in 2000



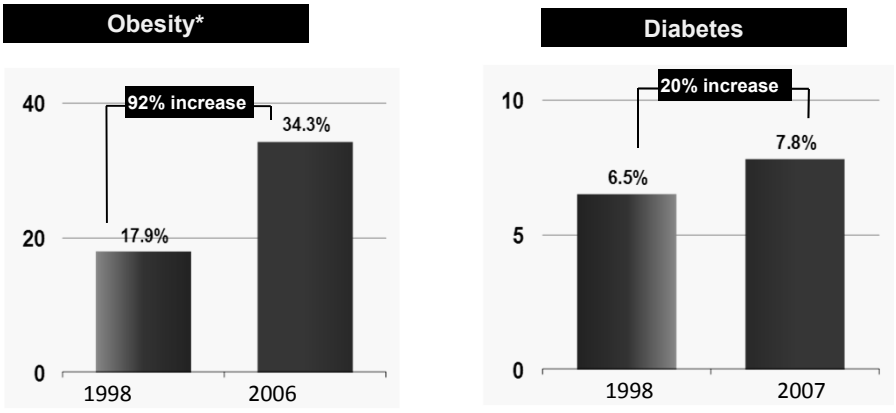
Narayan et al, JAMA, 2003

Type 2 Diabetes in Children and Adolescents

Diagnostic Blood Tests

RPG	FPG	OGTT	HbA_{1c} or A1C
Random plasma glucose	Fasting plasma glucose	Oral glucose tolerance test	Glycated hemoglobin Average of blood glucose over 2-3 months
Any time, irrespective of meals	Before breakfast (8-h fast)	1 or 2 hours after drinking a medically formulated glucose drink	Any time, irrespective of meals
≥200 mg/dL plus signs/symptoms	≥126 mg/dL	≥200 mg/dL	≥6.5%?
Diagnosis must be confirmed with a second glucose measurement on another day			New criterion (ADA, 2009) No confirmation necessary

Increasing Problem of Obesity and Diabetes in the United States



*BMI ≥30 kg/m^2.

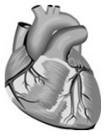
Mokdad AH, et al. *JAMA*. 1999;282:1519-1522; Ogden CL, et al. NCHS data brief no 1. Hyattsville, MD: National Center for Health Statistics, 2007; Mokdad AH, et al. *Diabetes Care*. 2000;23:1278-1283; CDC. National diabetes fact sheet. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2008.

Type 2 Diabetes

Why Is It Important?

Clinical Impact of Diabetes Mellitus

Heart disease and stroke
- **Account for 65% of deaths**
- **2- to 4-fold increase in cardiovascular disease death rates**



Kidney disease
- **Diabetes is leading cause of ESRD**
- **Accounts for 44% of cases**

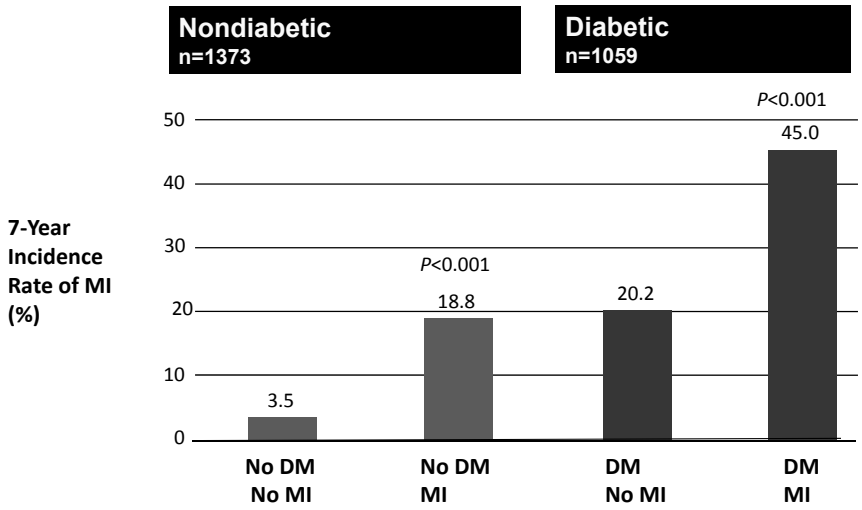
Diabetes

Blindness
- **Diabetic retinopathy causes 12,000 to 24,000 new cases of blindness/year**
- **Serves as leading cause of new cases of blindness in adults 20-74 years of age**

Amputations
- **More than 60% of nontraumatic lower-limb amputations occurs in people with diabetes**
- **10-fold increase in amputation rate**

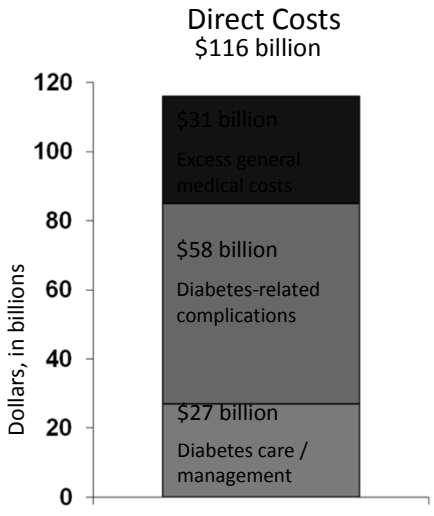
ESRD, end-stage renal disease.
American Diabetes Association. http://www.diabetes.org/diabetes-statistics/complications.jsp. Accessed December 11, 2008

Diabetes Is a Cardiovascular Disease Risk Equivalent



DM=diabetes mellitus; MI=myocardial infarction.
Haffner SM, et al. *N Engl J Med.* 1998;339:229-234.

Costs of Diabetes in the United States in 2007: 174 Billion



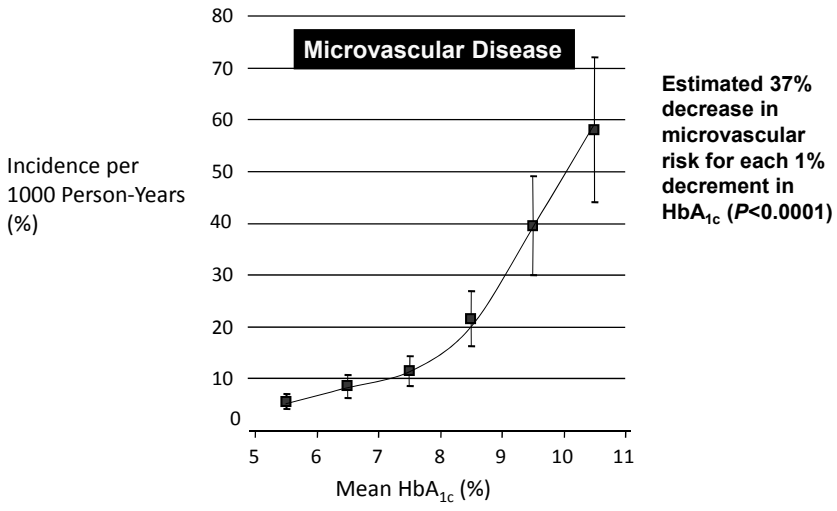
- **15 million work days absent**
- **120 million work days with reduced performance**
- **445,000 cases of unemployment disability in 2007**
  - **107 million work days lost due to diabetes-related unemployment disability**
- **Lost productivity due to premature, diabetes-related death: $26.9 billion**

American Diabetes Association. Costs of diabetes. Available at: http://www.diabetes.org/diabetes-statistics/cost-of-diabetes-in-us.jsp. Accessed March 11, 2009.

Type 2 Diabetes

How Do We Minimize Its Impact?

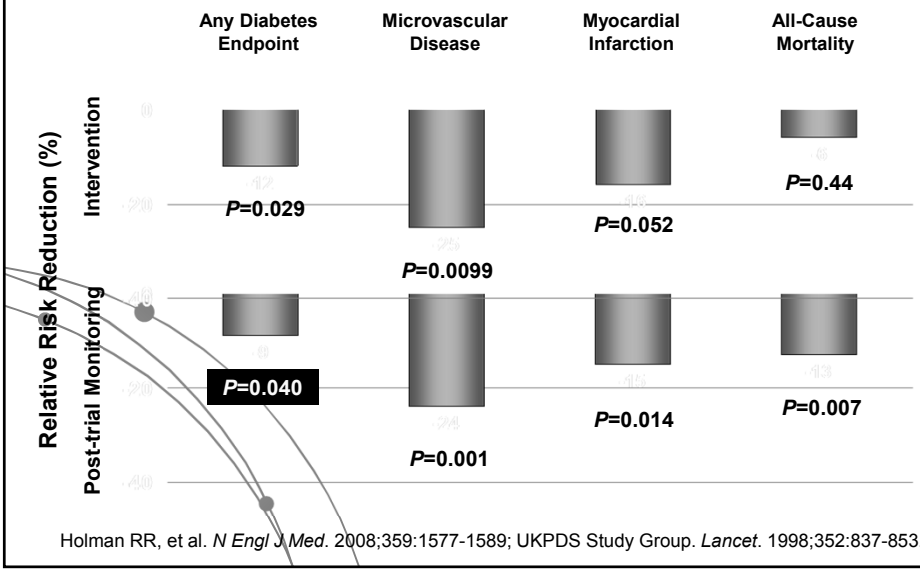
Historic Rationale for Improving Glycemia: Microvascular Risk Reduction



Estimated 37% decrease in microvascular risk for each 1% decrement in HbA_{1c} (*P*<0.0001)

Stratton IM, et al. *BMJ*. 2000;321:405-412.

Lasting Benefits of Early, Intensive Intervention: UKPDS "Legacy Effect"



Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589; UKPDS Study Group. *Lancet*. 1998;352:837-853.

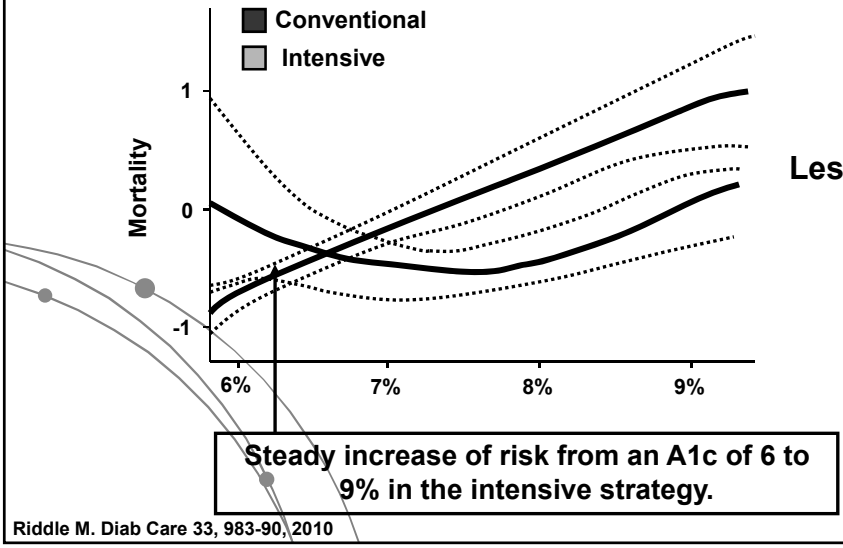
Early vs Late Intervention in Type 2 Diabetes

Early diagnosis and intensive glucose control therapy from the start are the key to long-term risk reduction in diabetes

				Macrovascular Benefit
UKPDS 80	Goal: FPG <108 mg/dL Intervention endpoint: 7.0% Follow-up: 7.7%	N=4209 17 yr	Newly diagnosed with T2DM	Yes
				No

BL=baseline; T2DM=type 2 diabetes mellitus. Holman RR, et al. *N Engl J Med*. 2008;359:1577-1589; ACCORD Study Group. *N Engl J Med*. 2008;358:2545-2559; ADVANCE Collaborative Group. *N Engl J Med*. 2008;358:2560-2572; Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.

Mortality Risk from the ACCORD Study



Lessons?

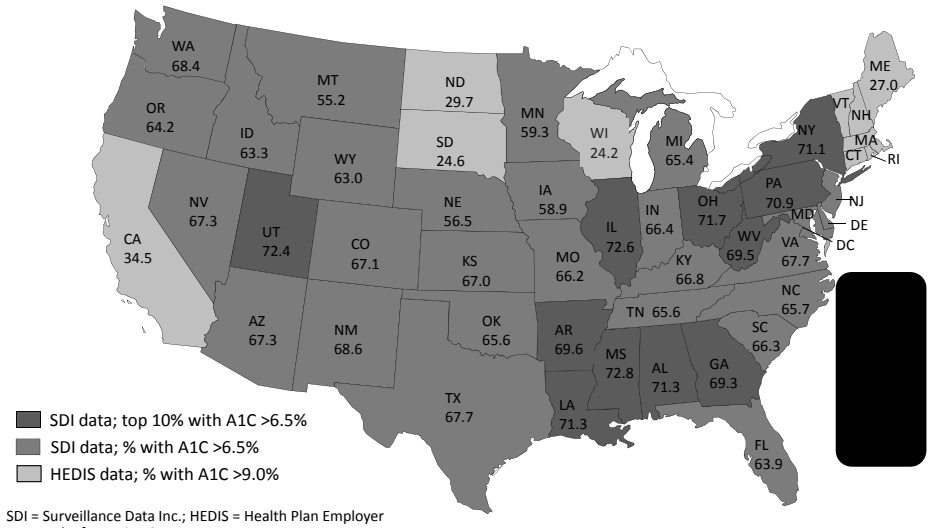
Riddle M. Diab Care 33, 983-90, 2010

ADA 2011

Type 2 Diabetes

How Successful Are We at Controlling Hyperglycemia?

AACE "State of Diabetes in America": 67% of Patients Have an A1C >6.5%

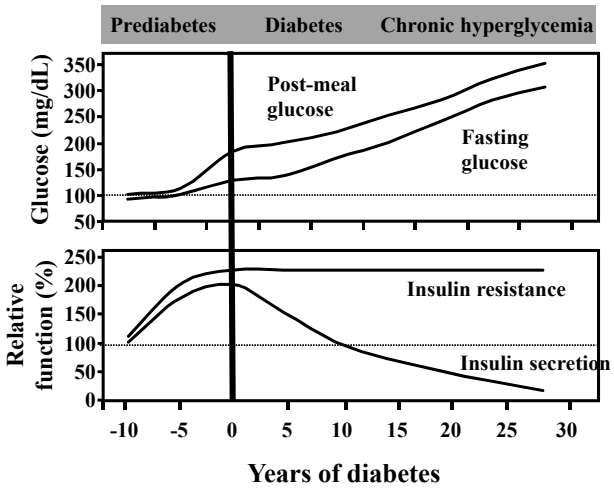


SDI = Surveillance Data Inc.; HEDIS = Health Plan Employer Data and Information Set

AACE. State of diabetes in America: striving for better control. Available at: http://www.stateofdiabetes.com/state_compare.htm. Accessed February 9, 2007

Pathophysiology of Diabetes

Natural History of Type 2 Diabetes



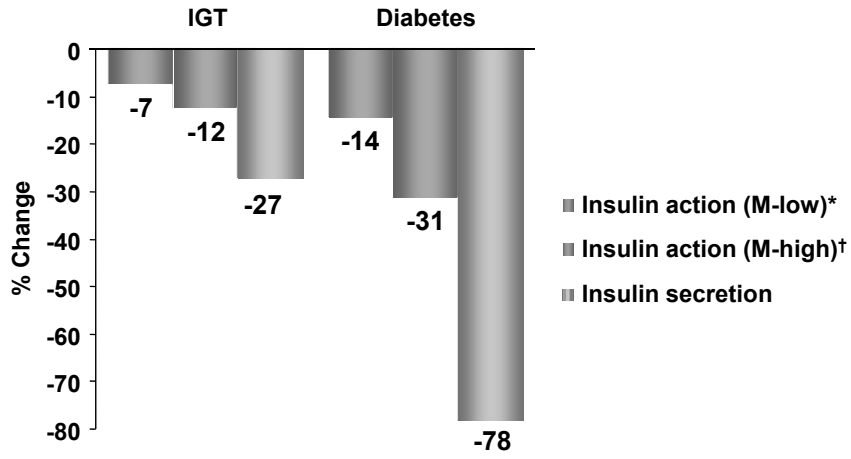
Insulin Resistance

- Inherited
  - Rare syndromes
  - Lipodystrophy
- Acquired
  - Obesity
  - Physical inactivity
  - Dietary
  - Glucose toxicity
  - Immunological
  - Drugs
- Other: HTN, PCOS

Adapted from International Diabetes Center (IDC) Minneapolis, Minnesota.

Lifestyle changes – diet and…

Insulin Resistance vs. Insulin Secretion

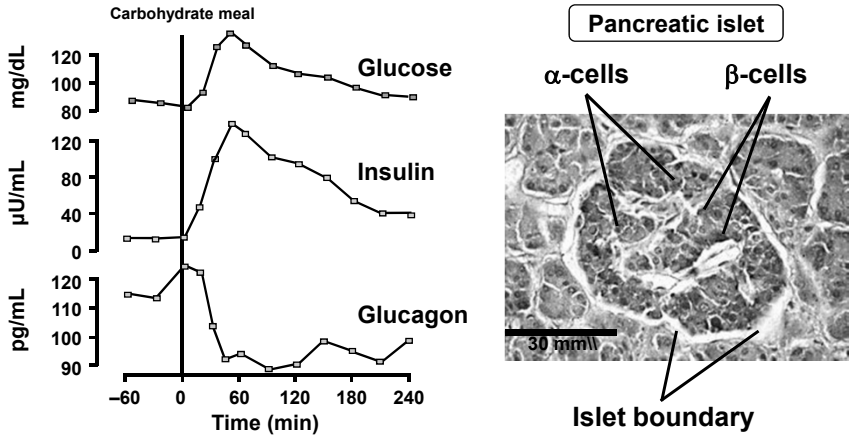


*M-low: euglycemic clamp at physiologic insulin levels (840 ± 252 pmol/L)
†M-high: euglycemic clamp at supraphysiologic insulin levels (13,332 ± 3,582 pmol/L);
Weyer C. et al. *J Clin Invest.* 1999;104:787-794.

EVERYTIME I FEEL LIKE EXERCISING……

I JUST LIE DOWN UNTIL THE FEELING PASSES….

Normal Insulin and Glucagon Response in the Postprandial Period



Photomicrograph courtesy of Michael Sarras, PhD, Rosalind Franklin University of Medicine and Science

Unger RH. *N Engl J Med.* 1971;285:443-449.

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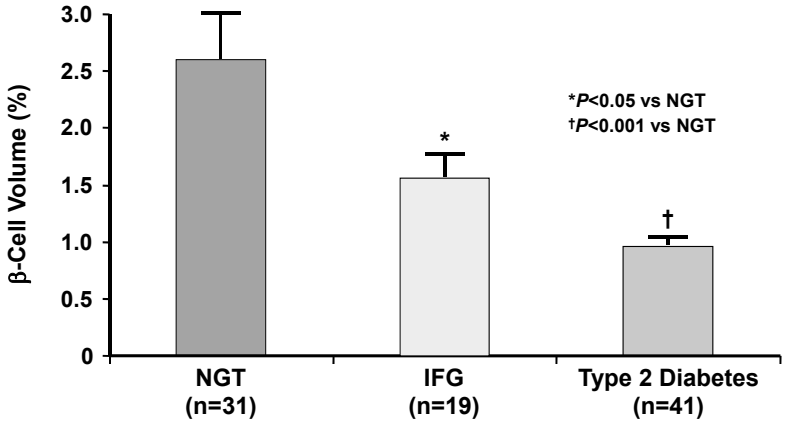
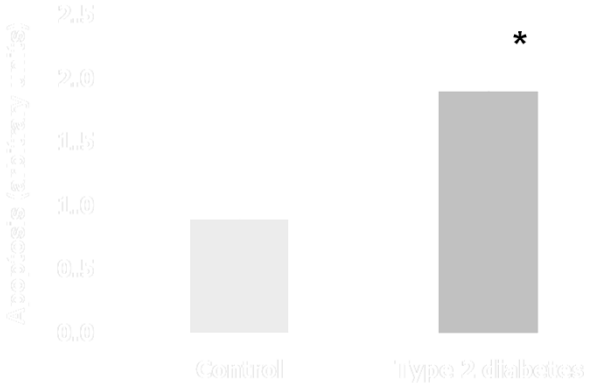
b-Cell Mass in Type 2 Diabetes Patients and Controls



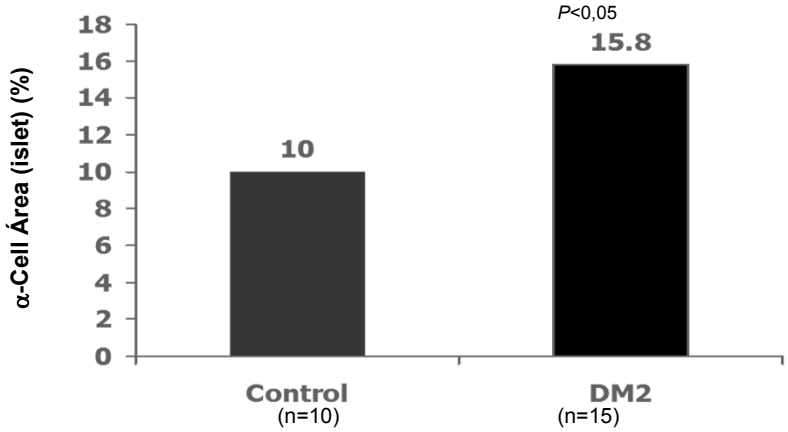
Butler A, et al. *Diabetes*. 2003;52:102-110.

Increased Beta-Cell Apoptosis Occurs in Type 2 Diabetes



*p<0.05. Islet cell death was assessed by an ELISA method, which evaluates the cytoplasmic histone-associated DNA fragments. After incubation absorbance of samples was read spectrophotometrically.
Data obtained from pancreatic islets isolated from 6 T2DM organ donors and 10 nondiabetic cadaveric organ donors.
Adapted from Marchetti P et al. *J Clin Endocrinol Metab*. 2004;89:5535–5541.

In Type 2 Diabetes, The α-Cell Mass is Increased



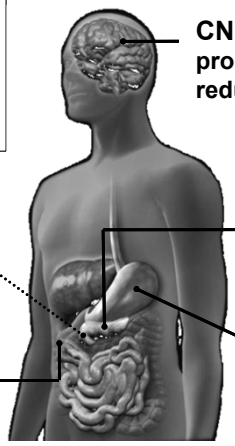
Clark A, et al. *Diabetes Res*. 1988;9:151-159.

GLP-1 – Effects in Humans
Understanding the Potential of Incretins

Normal GLP-1 secretion
- **Stimulated by food intake**
- **Diminished in IGT, diabetes**
- **Response to GLP-1 preserved even in diabetes**

Liver:
↓ glucagon reduces hepatic glucose output

Alpha cell:
↓ glucagon secretion post-meal



CNS:
promotes satiety and reduction of appetite

Beta cell:
enhances *glucose-dependent insulin* secretion

Stomach:
regulates gastric emptying

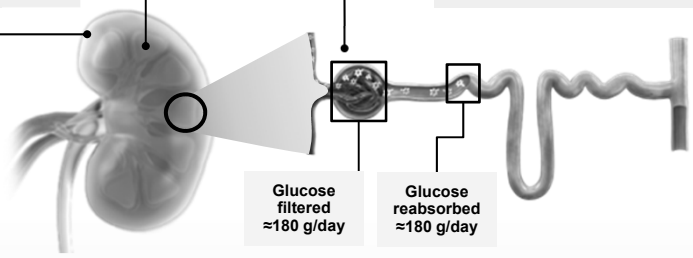
Flint A et al. *J Clin Invest.* 1998;101:515-520. Larsson H et al. *Acta Physiol Scand.* 1997;160:413-422
Nauck MA et al., *Diabetologia.* 1996;39:1546-1553. Drucker DJ. *Diabetes.* 1998;47:159–169.

The Kidney Supports Three Key Functions in Glucose Handling

1. Kidney Glucose Production in the Renal Cortex

2. Kidney Glucose Utilization in the Renal Medulla

3. Kidney Glucose Reabsorption in Nephrons



Glucose filtered ≈180 g/day

Glucose reabsorbed ≈180 g/day

In Healthy Subjects

FFA=free fatty acid.
Gerich JE. *Diabet Med.* 2010;27:136-142.

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CNS Regulation of Weight

- Weight is controlled via a multi level system involving gut and adipose origin hormones which input into the CNS and affect hunger, sensory perception, cognition, emotion and behavior.

NEUROTRANSMITTER ABBREVIATION

- **POMC Proopiomelanocortin**
- **CART Cocaine and Amphetamine regulated transcript**
- **Alpha MSH alpha melanocyte stim hormone**
- **MC3R,MC4R Melanocortin 3,4 receptors**
- **NPY Neuropeptide Y**
- **AgrP Agouti related peptide**
- **Y1R Y5R Receptors for NPY AgRP**
- **MCH Melanin Concentrating Hormone**

HUNGER SIGNALING 1

ANOREXIGENS	OREXIGENS
HYPOTHALAMUS (Arcuate Nucleus)	**HYPOTHALAMUS (Arcuate Nucleus)**
POMC, Alpha MSH	NPY
CART	AgRP
Serotonin	
HYPOTHALAMUS (Paraventricular Nucleus)	**HYPOTHALAMUS(Lateral)**
CRH, TRH,CART	MCH
Neurotensin, Neurotrophic factor	Orexin/Hypocretin

HUNGER SIGNALING 2

ANOREXIGENS	OREXIGENS
GUT	**GUT**
CCK	Ghrelin
GIP	
PYY	
Oxyntomodulin	
GLP1	

HUNGER SIGNALING 3

ANOREXIGENS	OREXIGENS
PANCREAS	
Pancreatic Polypeptide	
ADIPOSE TISSUE	
Leptin	
Adiponectin	

Pathogenesis of Type 2 Diabetes
An Evolving Concept