

***A New Paradigm
in the Treatment of
Type 2 Diabetes***

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Disclosures

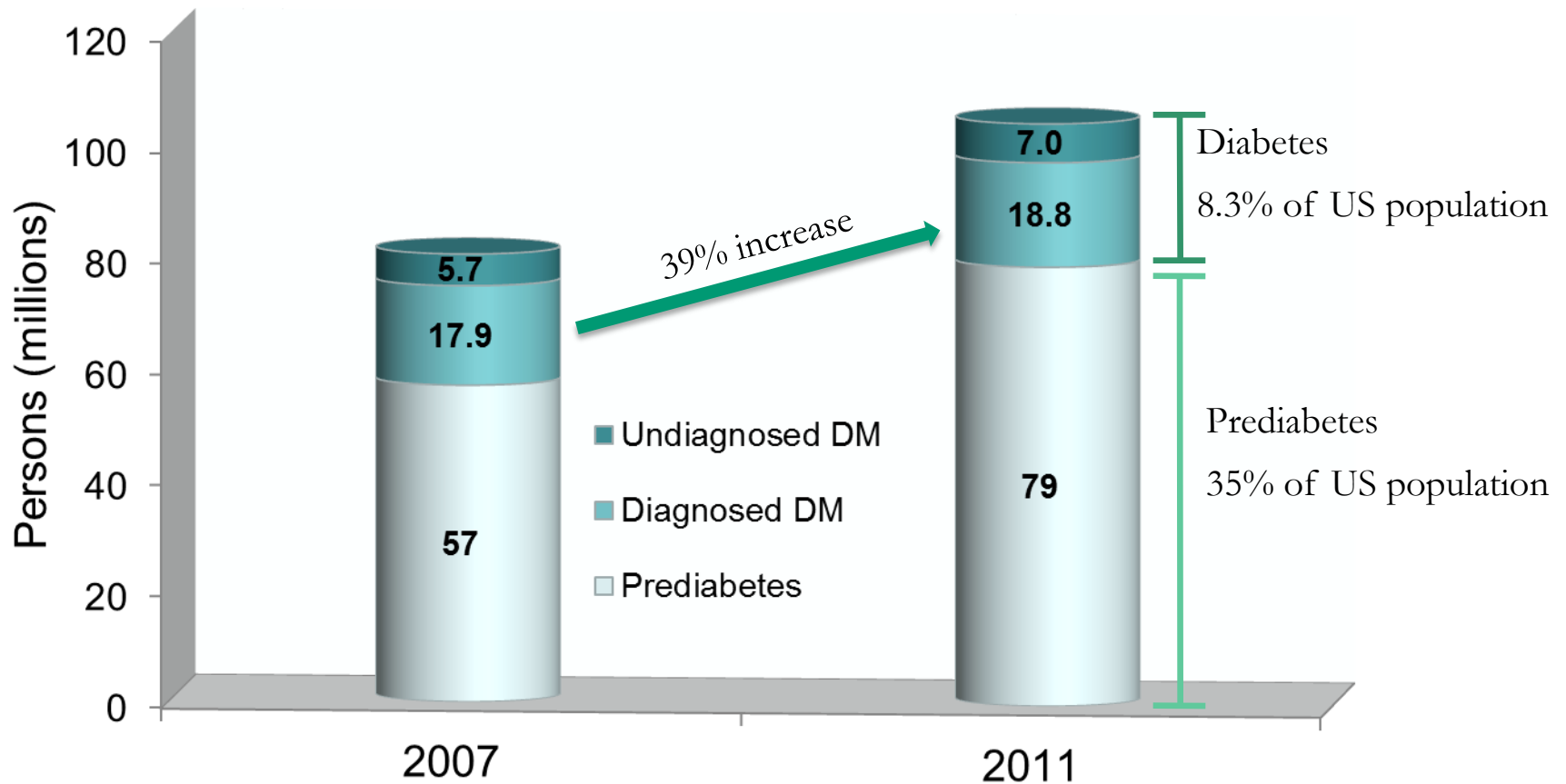
The presenter is on speaker bureau for the following companies:

- ***Warner Chilcott***
- ***Santarus***
- ***Eli Lilly***
- ***Boehringer Ingelheim***
- ***Novo Nordisk***
- ***AstraZeneca***
- ***Bristol-Myers Squibb***
- ***Pfizer***
- ***Sanofi-Aventis***
- ***Janssen***
- ***Amarin***
- ***Vivus***

***At the End of This Activity,
Participants Will Be Able To Understand:***

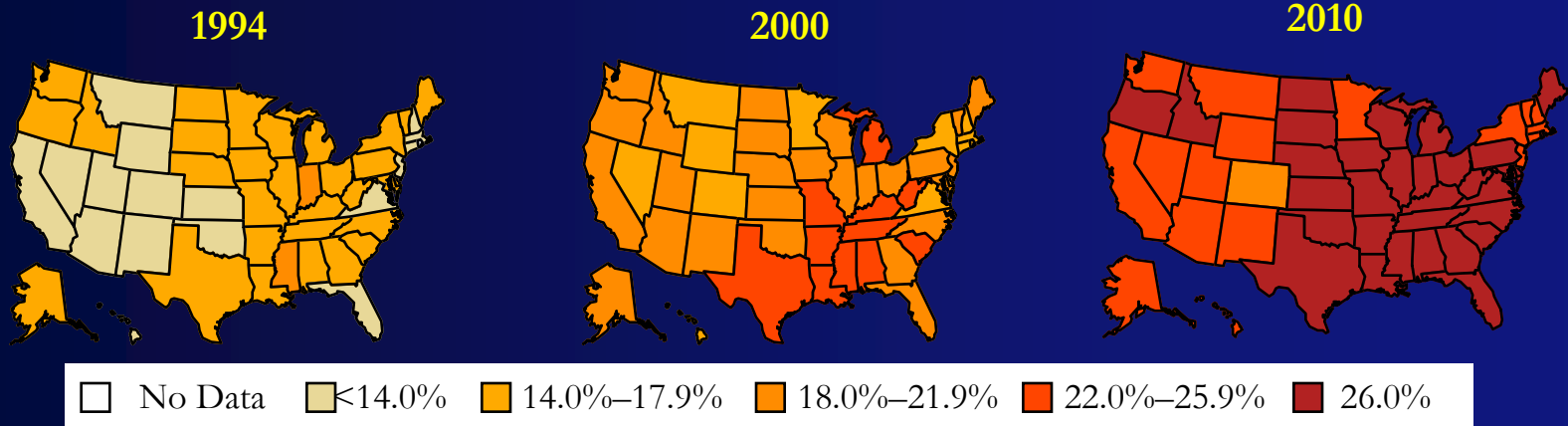
- ***The natural history of Type 2 Diabetes***
- ***Organs involved in the development of glucose intolerance in Type 2 Diabetes***
- ***Why therapy for Type 2 Diabetes should be based on pathophysiology***

Prevalence of Diabetes and Prediabetes in the United States

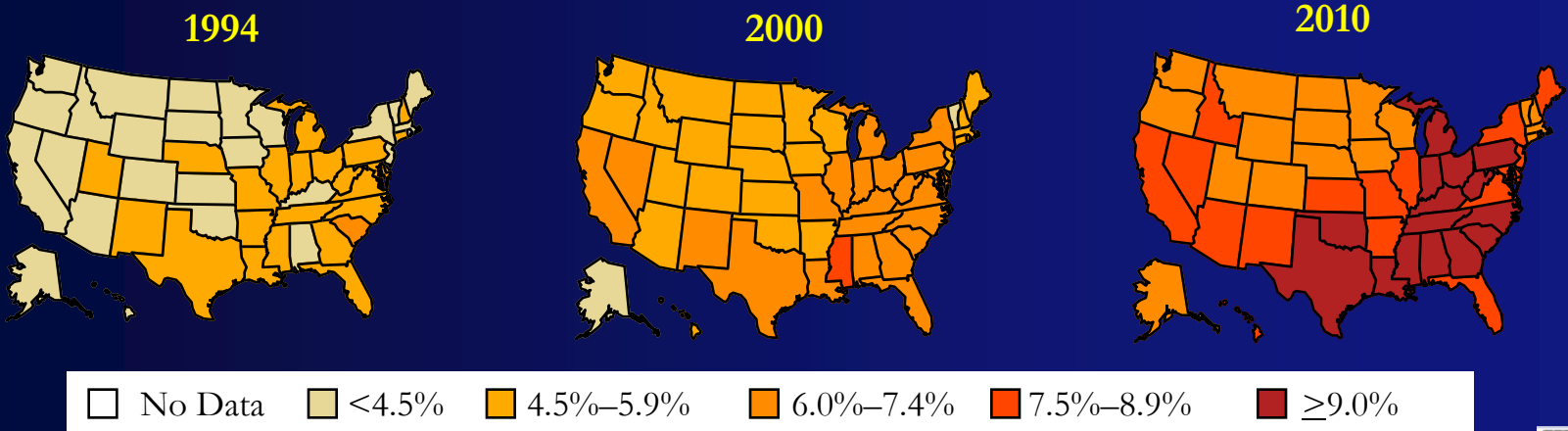


Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults Aged 18 Years or Older

Obesity (BMI ≥ 30 kg/m²)



Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at

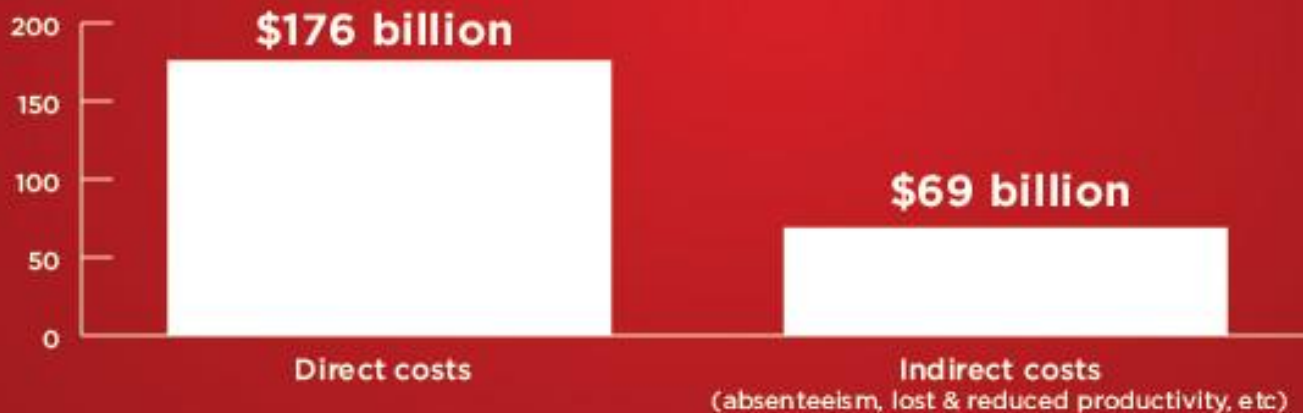
<http://www.cdc.gov/diabetes/statistics>



The Costs of Diabetes Are Escalating Rapidly in the United States – Up 41% Since 2007

\$245 BILLION

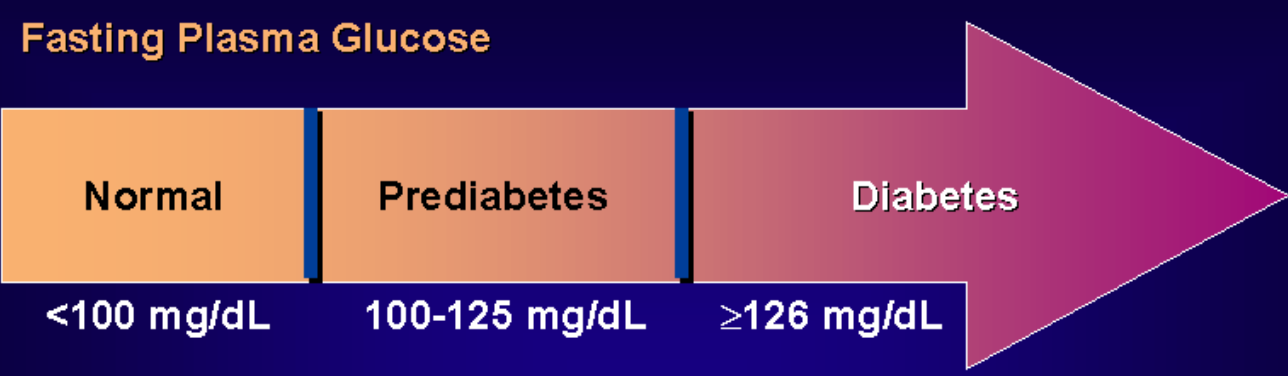
TOTAL COST OF DIAGNOSED DIABETES IN THE UNITED STATES IN 2012.



Sources: American Diabetes Association

***Prediabetes and
Diabetes***

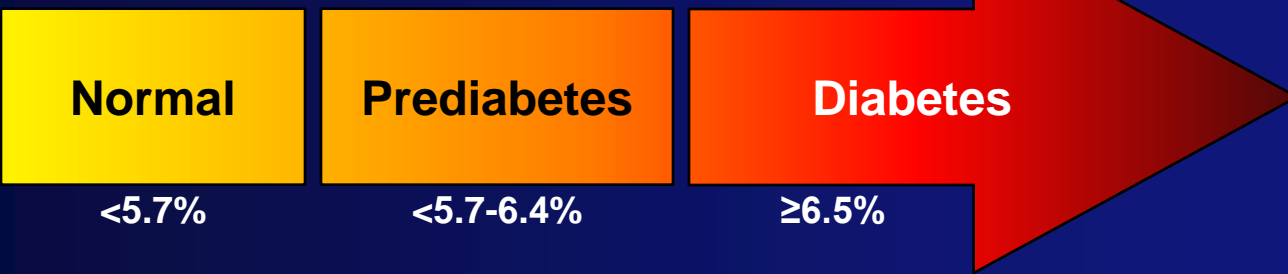
Diagnosing Prediabetes and Diabetes Mellitus



Over a period of 5 years, 30% of pre-diabetics will develop diabetes



50% higher risk of CVD: CAD and stroke



Diabetes Prevention Program Outcomes Study (DPPPOS)

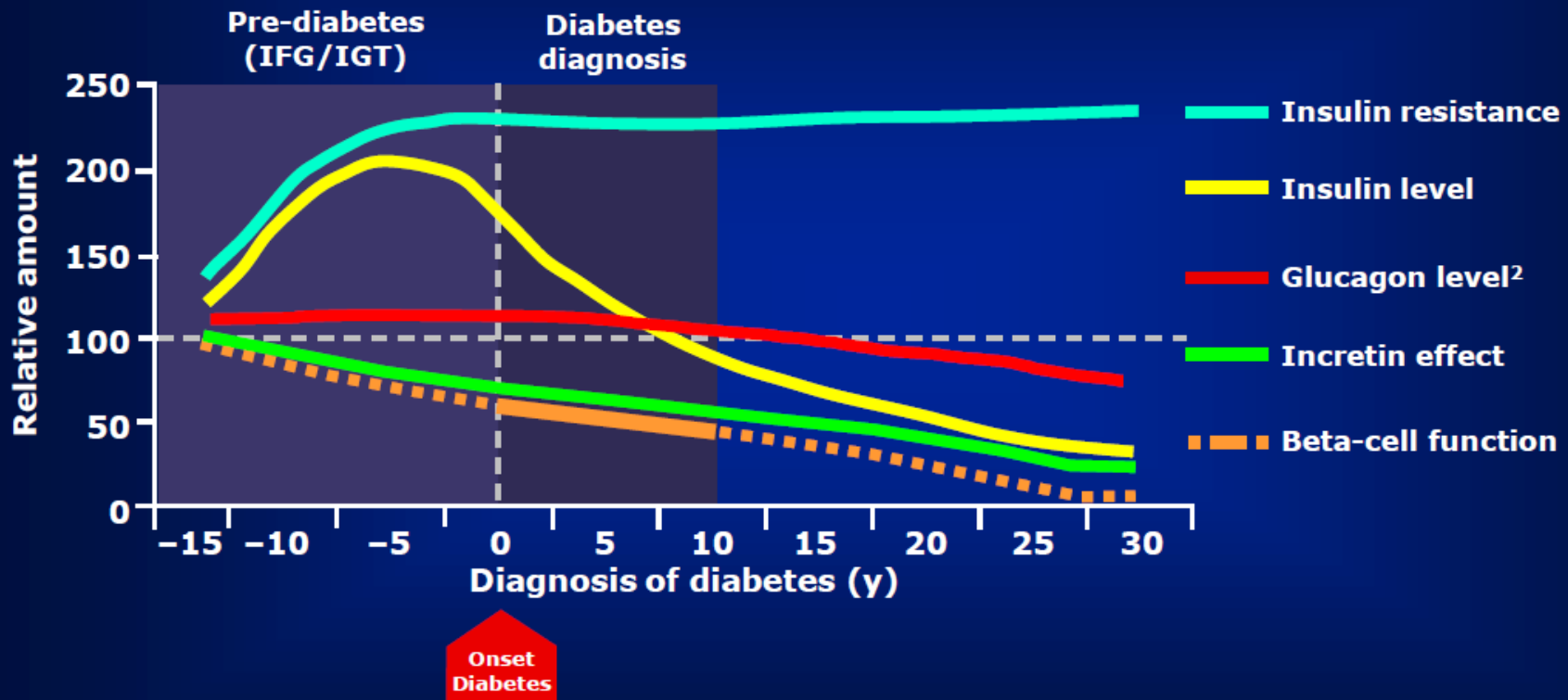
- **8% of participants with pre-diabetes had diabetic eye disease (retinopathy)**
- **12.6% of participants with type 2 diabetes who developed diabetes during the DPP had diabetic eye disease**

These findings suggest that patients with pre-diabetes or newly diagnosed type 2 diabetes should be screened for retinopathy.

DPP Research Group. Diabetic Medicine 2007; 24 (2); 137-144.

***Pathophysiology
of
Diabetes***

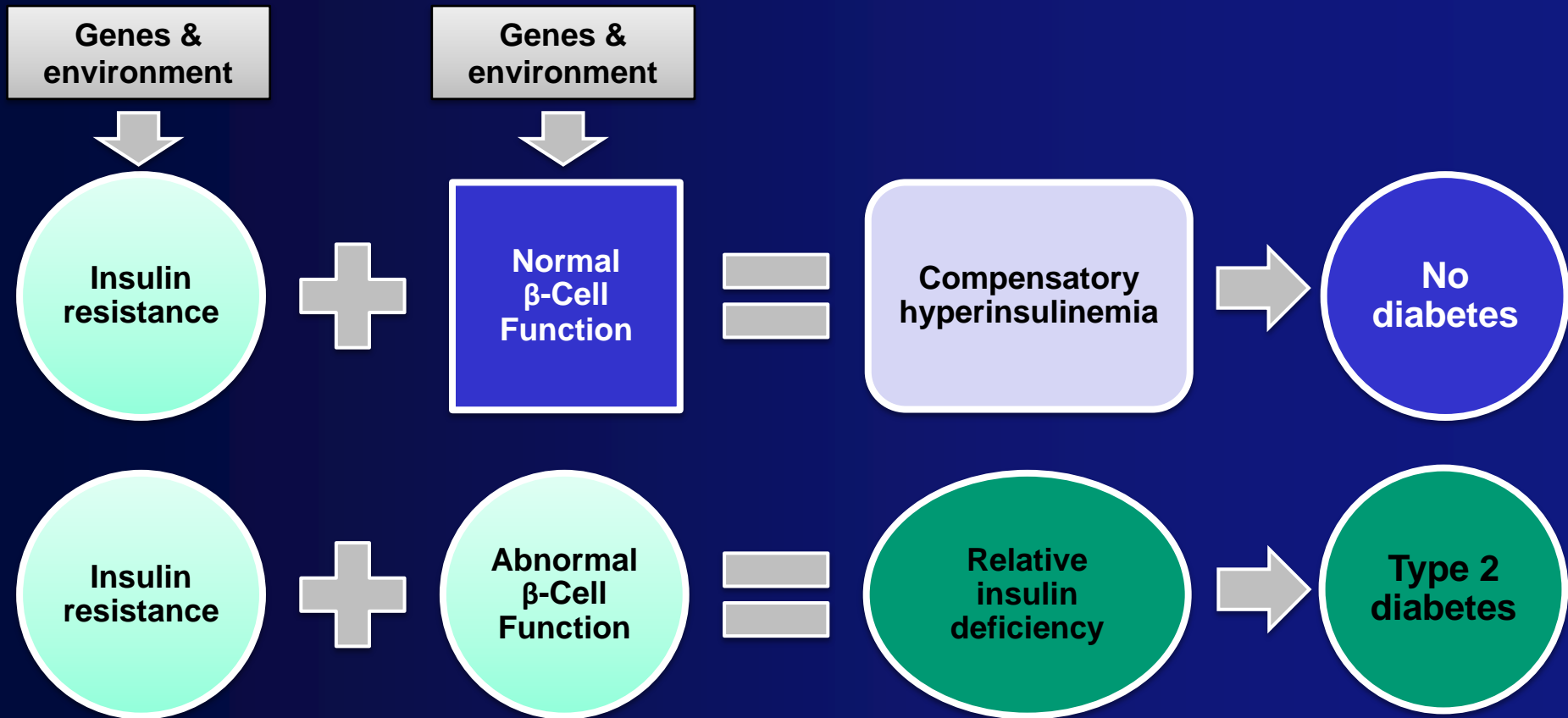
Type 2 Diabetes Is a Progressive Disease Involving Multiple Metabolic Abnormalities¹



IFG=impaired fasting glucose; IGT=impaired glucose tolerance.

1. Kendall DM et al. *Am J Med.* 2009;122(6A):S37-S50. 2. Gromada J et al. *Endocr Rev.* 2007;28(1):84-116.

Development of Type 2 Diabetes Depends on Interplay Between Insulin Resistance and β -Cell Dysfunction



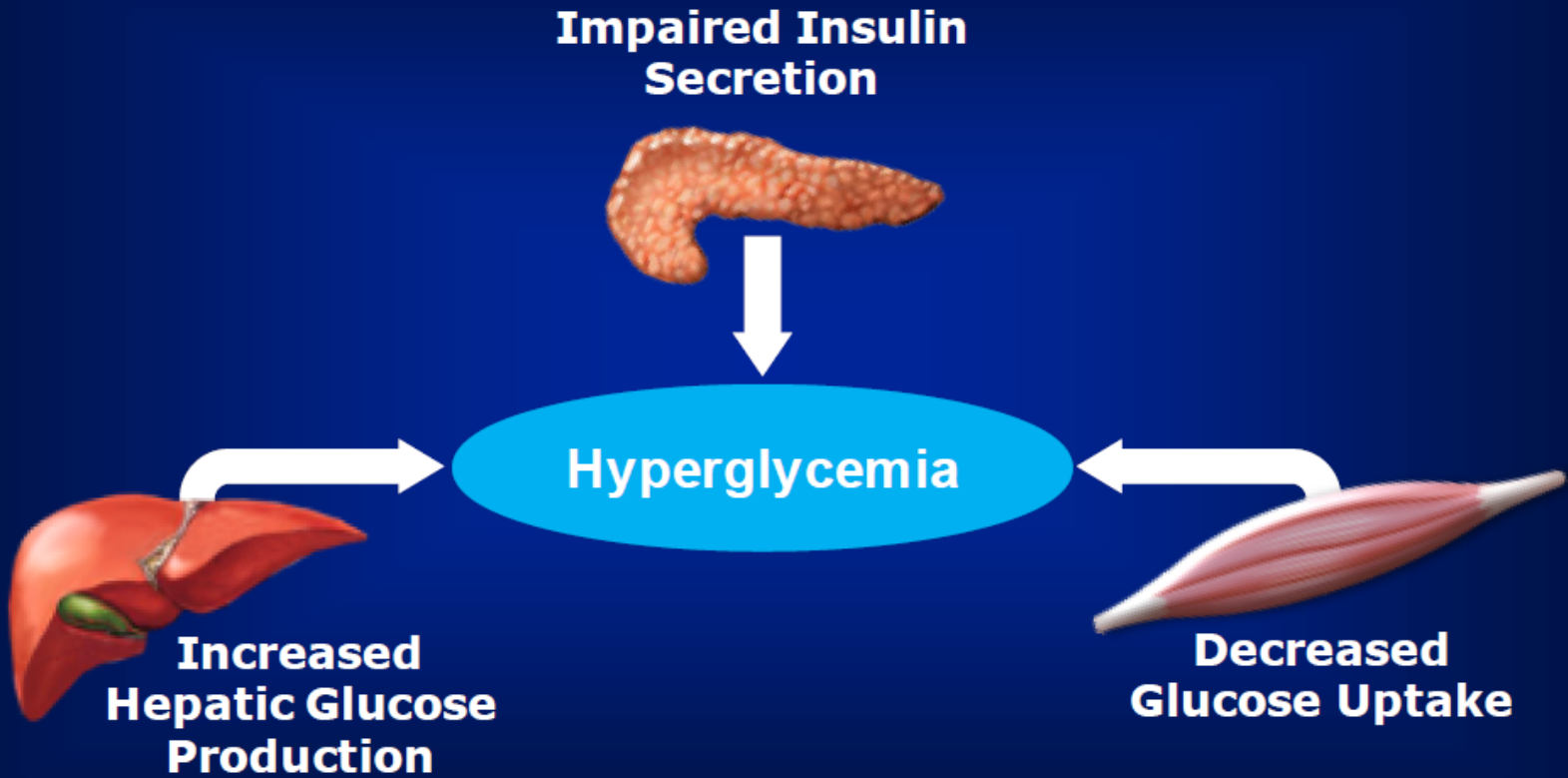
Pathogenesis of β -cell Failure

- ***Age***
- ***Genes***
- ***Insulin Resistance***
- ***Lipotoxicity***
- ***Glucotoxicity***
- ***Amyloid Deposition***
- ***Incretins***

Insulin Resistance

- ***Fasting State***
 - ***Hepatic Insulin Resistance***
 - ***Increased Hepatic Glucose Production (HGP)***
- ***Insulin Stimulated State***
 - ***Muscle***
 - ***Insulin Signal Transduction***

Pathogenesis of Type 2 Diabetes: The Triumvirate



Dysharmonious Quartet

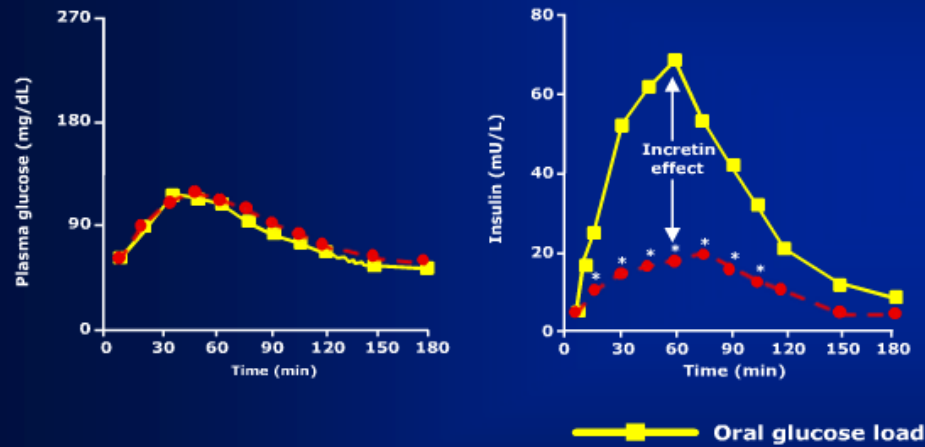
- **Liver**
- **β -cell**
- **Muscle**
- **Fat Cell**
 - **↑ Free fatty acid**
 - **↑ Glucose toxicity**
 - **↓ Insulin secretion**
 - **↓ Adiponectin**
 - **↓ Muscle sensitivity**
 - **↑ Insulin resistance**

Quintessential Quintet

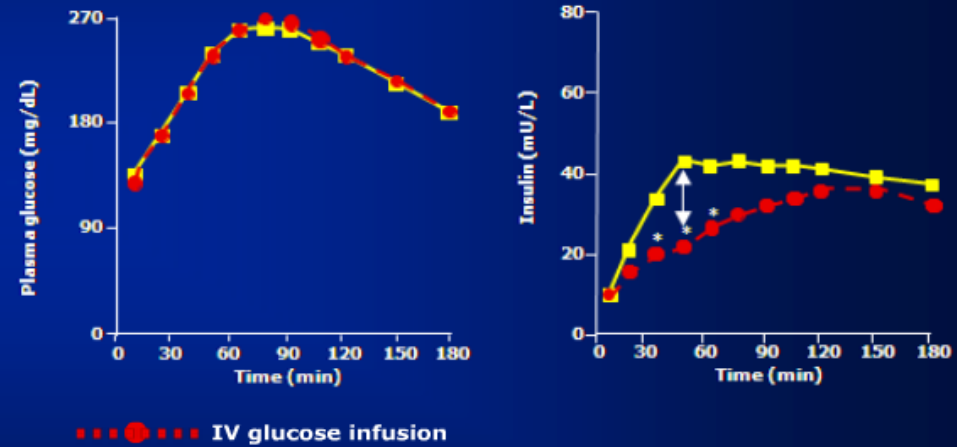
- **Liver**
- **β -cell**
- **Muscle**
- **Fat Cell**
- **Gastrointestinal Tissue**
 - **\uparrow GLP-1**
 - **\uparrow GIP**

Incretin Effect – Enhanced Insulin Response After Oral vs Intravenous Glucose - Is Impaired in Type 2 Diabetes

Incretin Effect in Healthy Controls



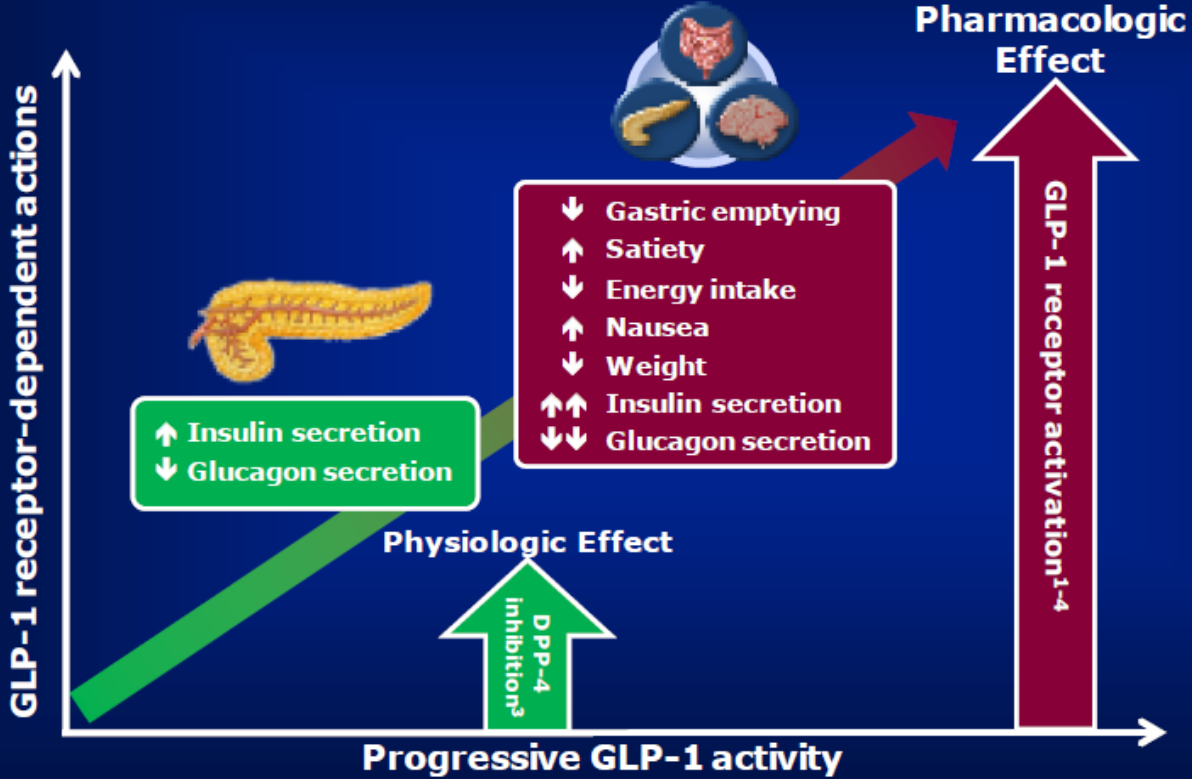
Impaired Incretin Effect in Type 2 Diabetes



* $P \leq 0.05$ compared with respective value after oral load.

Reproduced from Nauck M et al. *Diabetologia*. 1986;29(1):46-52.

Additional Physiologic Benefits Are Observed at Pharmacologic Levels of GLP-1

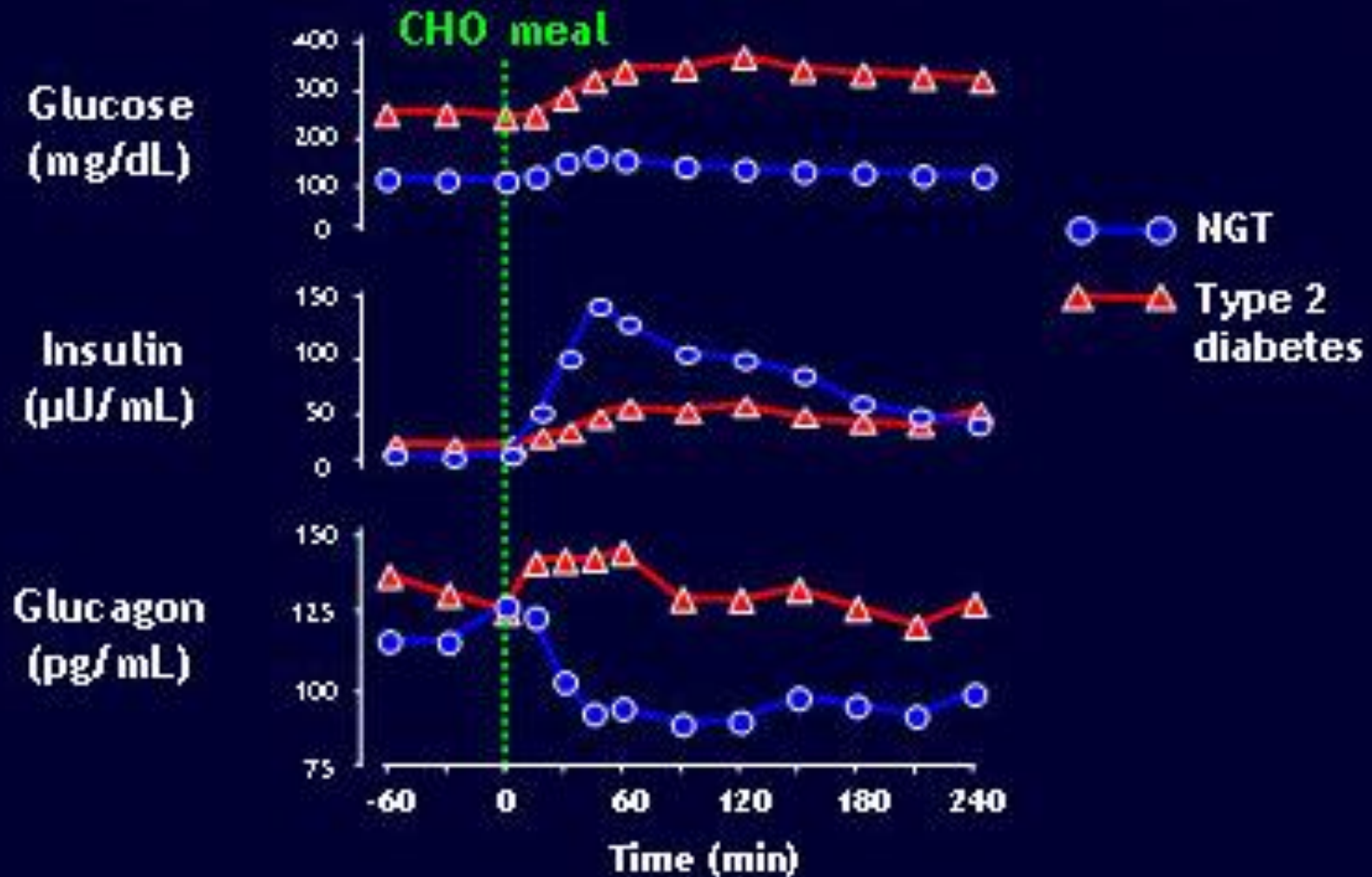


1. Wajchenberg BL. *Endocr Rev.* 2007;28(2):187-218. 2. Drucker DJ. *Diabetes Care.* 2003;26(10):2929-2940. 3. Baggio LL, Drucker DJ. *Gastroenterology.* 2007;132(6):2131-2157. 4. Drucker DJ, Nauck MA. *Lancet.* 2006;368(9548):1696-1705.

Setaceous Sextet

- **Liver**
- **β -cell**
- **Muscle**
- **Fat Cell**
- **Gastrointestinal Tissue**
- **α Cell**
 - **\uparrow Fasting glucagon**
 - **\uparrow HPG**

Defective Postmeal Insulin and Glucagon in Type 2 Diabetes

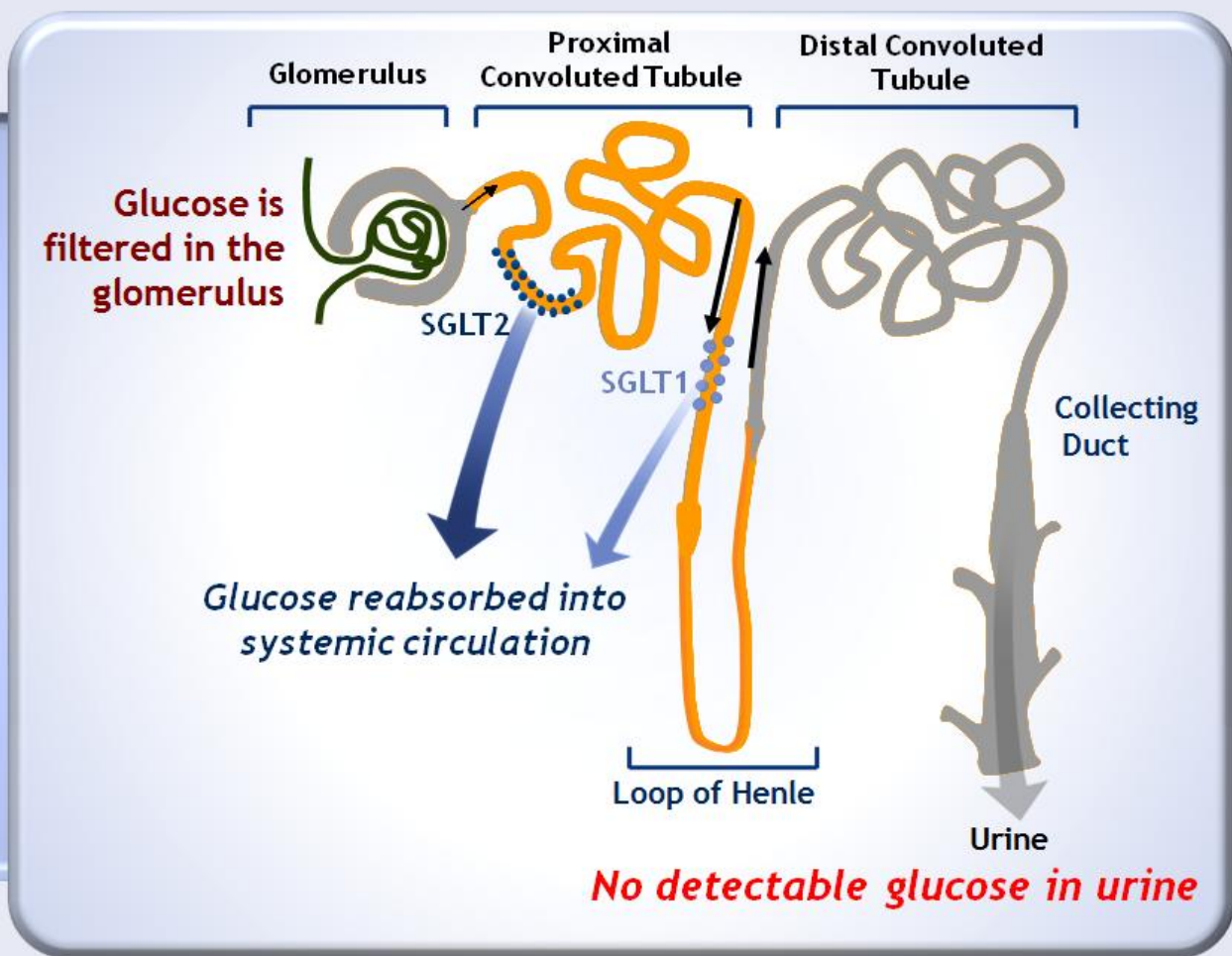


Septicidal Septet

- **Liver**
- **β -cell**
- **Muscle**
- **Fat Cell**
- **Gastrointestestinal Tissue**
- **α Cell**
- **Kidney**
 - **\uparrow SGLT2-receptor activity**

Sodium-Glucose Co-transporters (SGLTs) and Normal Renal Handling of Glucose

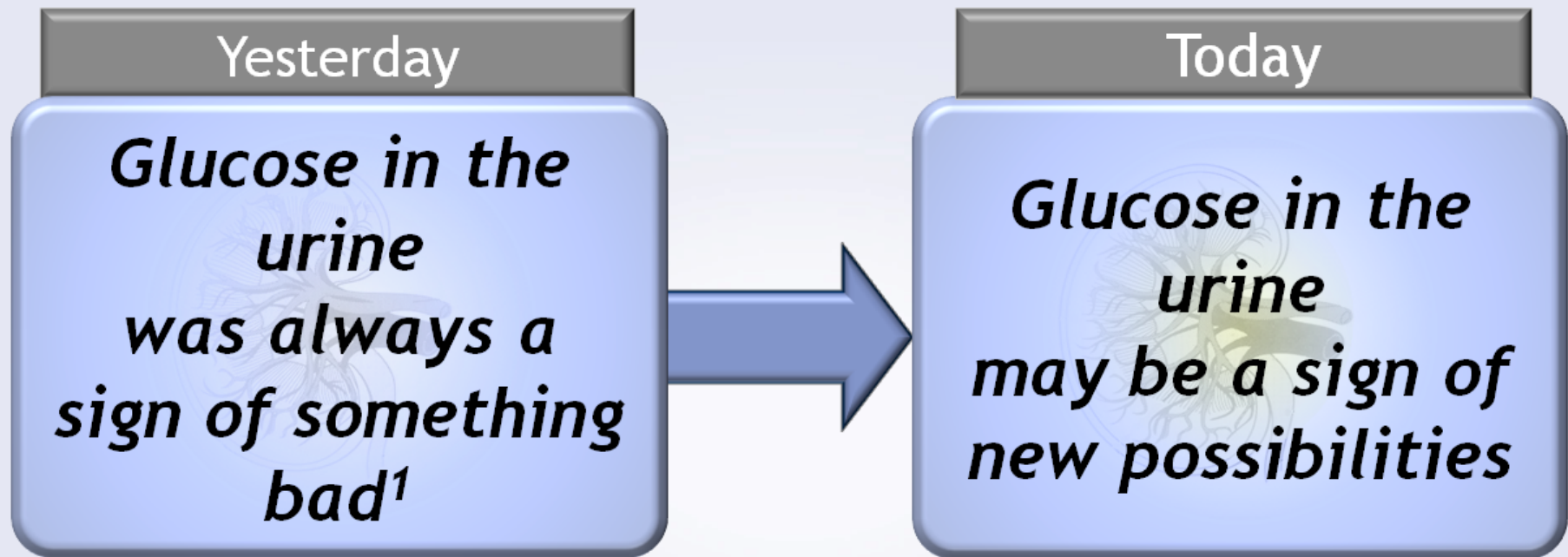
- 180 g/day/1.73 m² is filtered glucose load¹
- SGLT2 transports 90% of filtered glucose out of the tubular lumen¹⁻⁴
- SGLT1 transports the remaining 10% of filtered glucose¹⁻⁴
 - SGLT1 is the primary SGLT in the small intestine^{1,2}



SGLT = sodium-glucose co-transporter.

1. Wright EM et al. *J Intern Med.* 2007;261(1):32-43. 2. Kanai Y et al. *J Clin Invest.* 1994;93(1):397-404. 3. You G et al. *J Biol Chem.* 1995;270(49):29365-29371. 4. Wright EM. *Am J Physiol Renal Physiol.* 2001;280(1):F10-F18.

Changing Paradigms

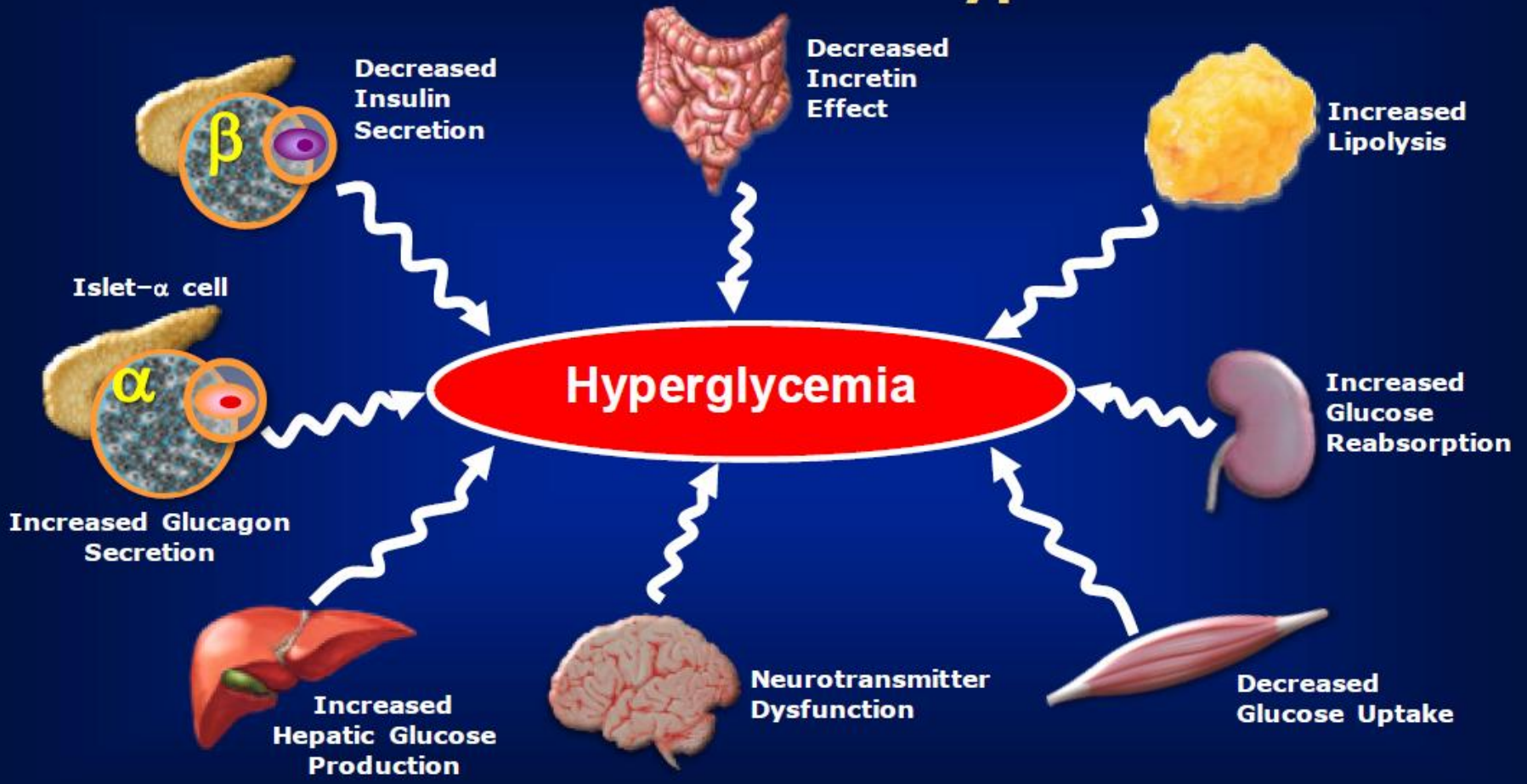


1. Cowart SL, Stachura ME. In: Walker HK et al, eds. *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 2. INVOKANA™ [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2013.

Ominous Octet

- **Liver**
- **β -cell**
- **Muscle**
- **Fat Cell**
- **Gastrointestinal Tissue**
- **α Cell**
- **Kidney**
- **Brain**
 - **\uparrow Cerebral insulin resistance**
 - **\uparrow SGP**
 - **\downarrow Muscle glucose uptake**

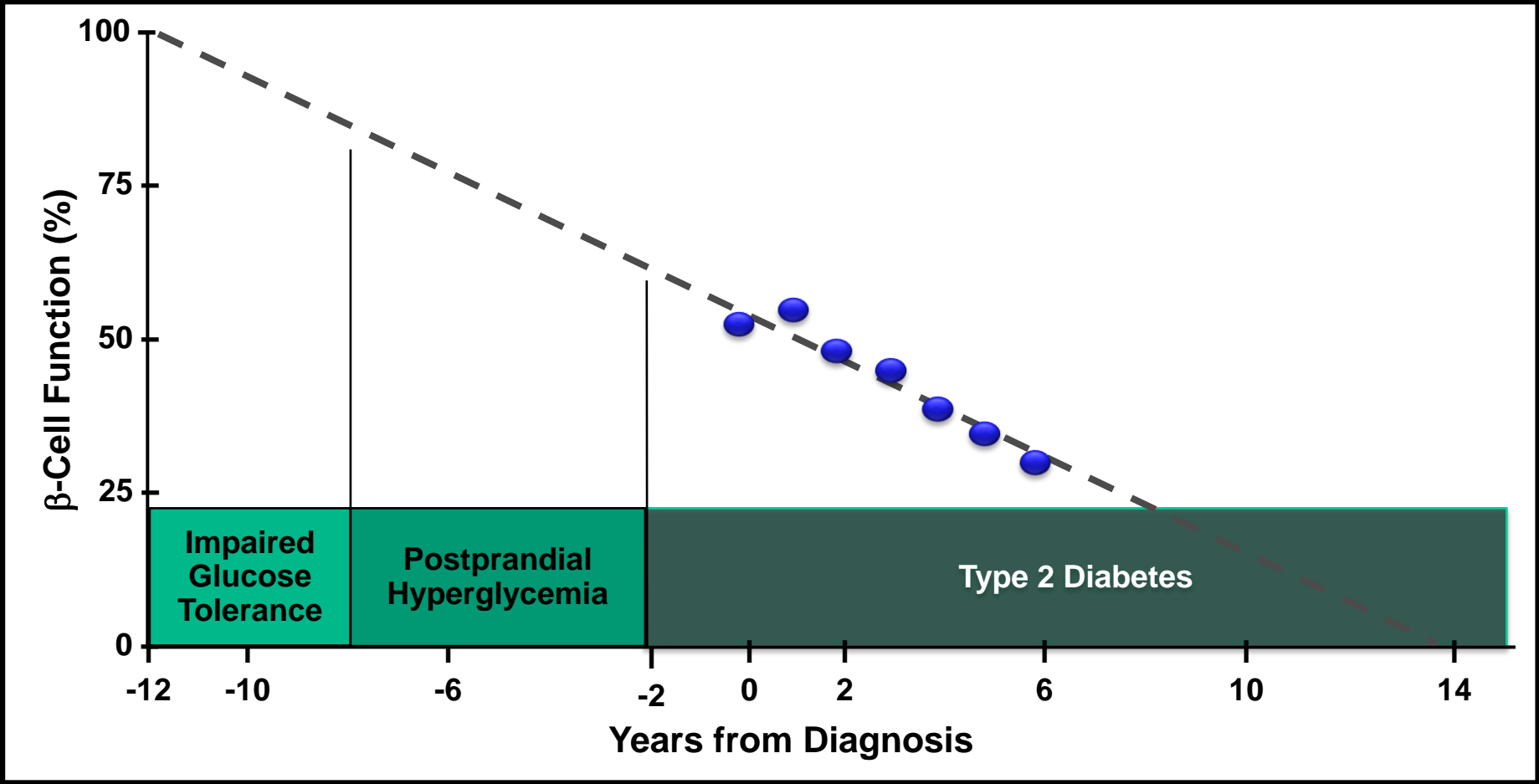
Ominous Octet: Core Defects in Type 2 Diabetes



Reproduced from DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

What have we learnt so far?

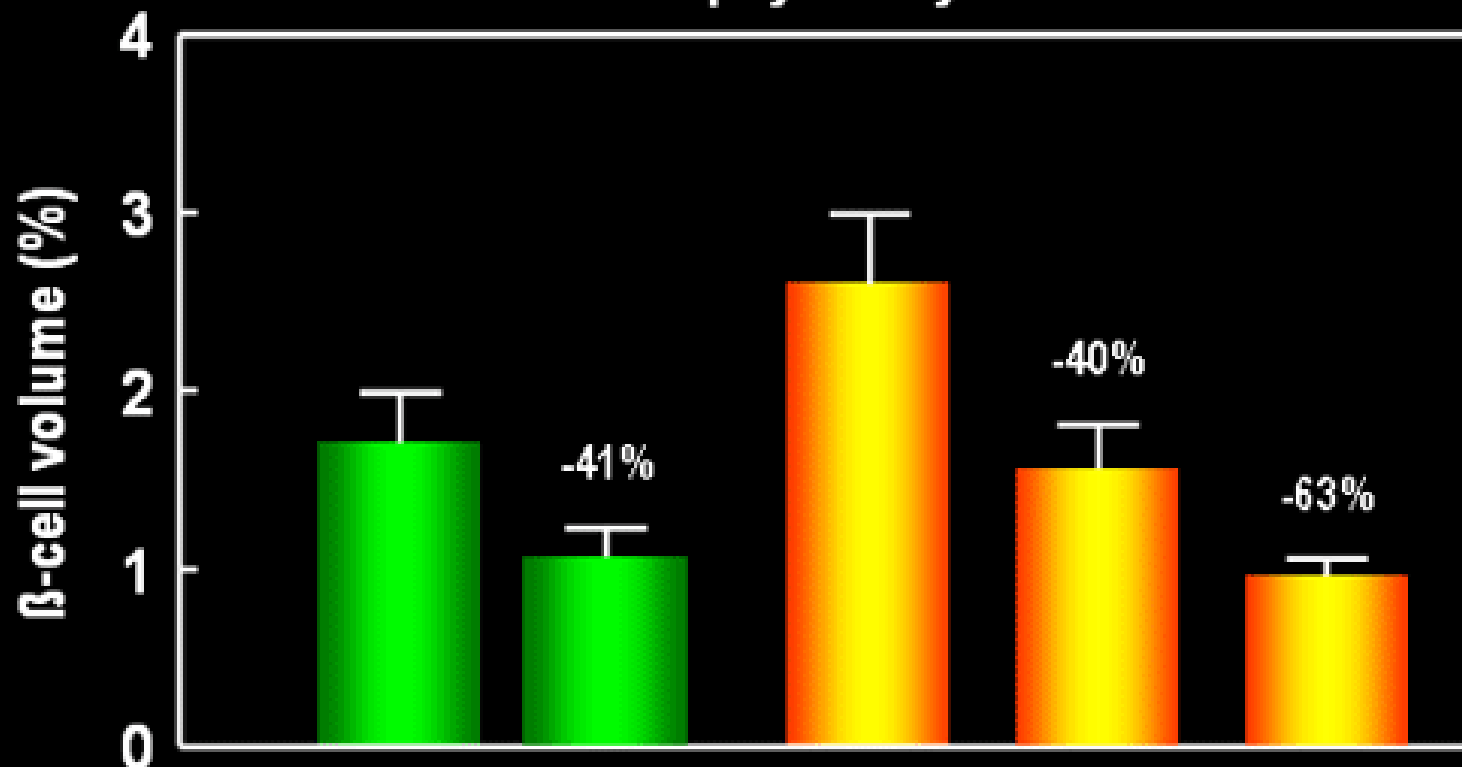
UKPDS: β -cell Loss Over Time



Dashed line = extrapolation based on Homeostasis Model Assessment (HOMA) data.
Data points from obese UKPDS population, determined by HOMA model.
Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl):S21-S25.

β -Cell Mass is Lower in IFG and Diabetes

An Autopsy Study



Body Habitus:

Lean

Obese

Fasting Glucose:

Normal

Diabetic

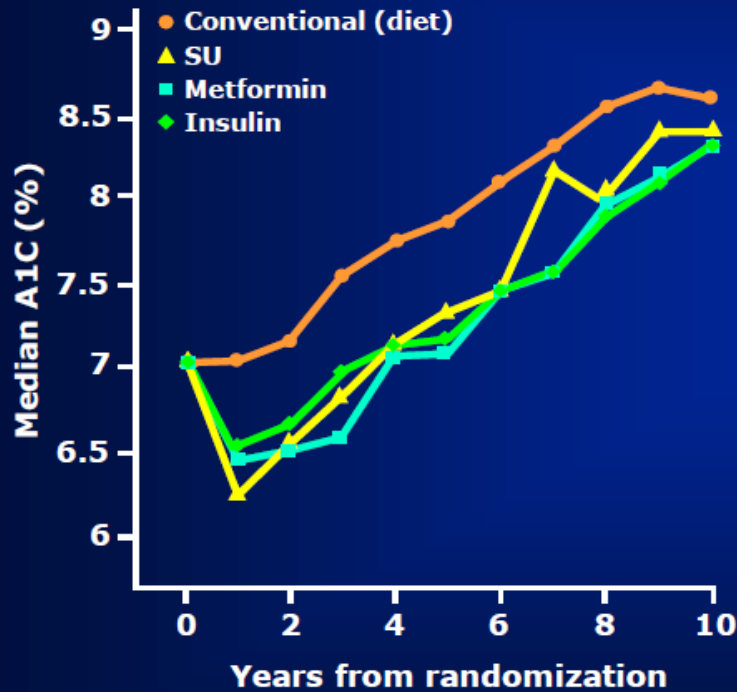
Normal

Impaired

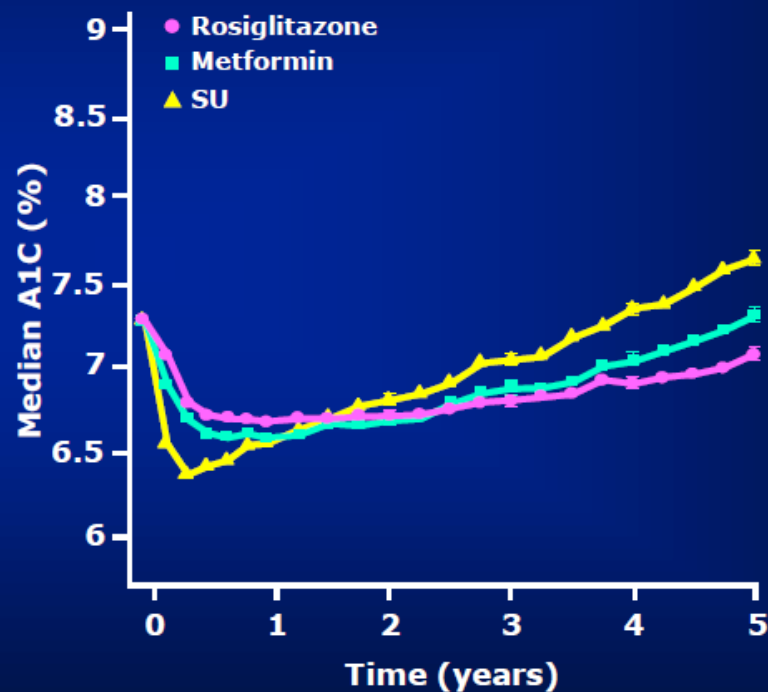
Diabetic

Type 2 Diabetes Is Progressive and Glycemic Control Usually Deteriorates Over Time

UKPDS (N=1439*)¹



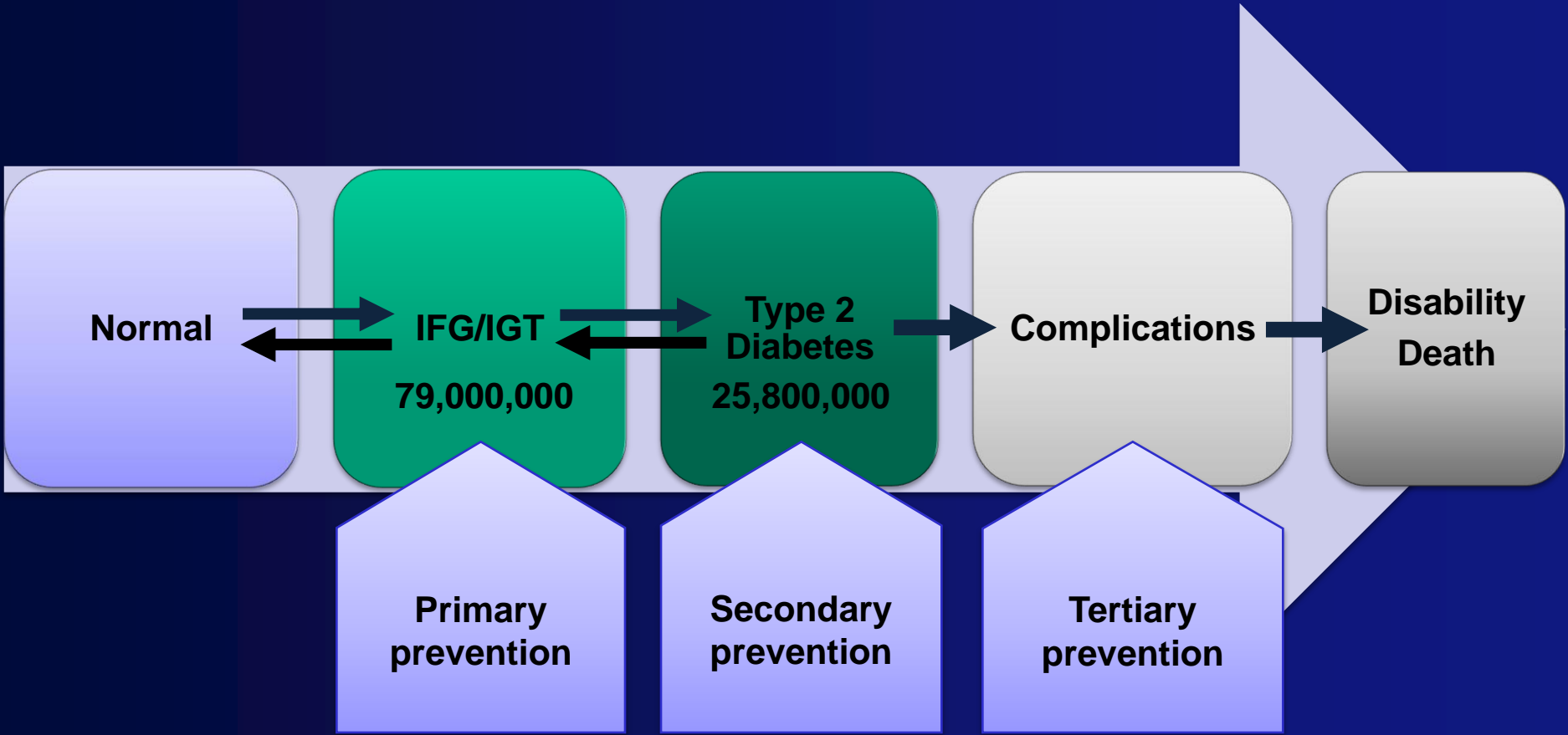
ADOPT (N=4351)²



* Data for 265 chlorpropamide-treated patients not shown.

1. Reproduced from UKPDS 34. *Lancet* 1998;352(9131):854-865. 2. Reproduced from Kahn SE et al. *N Engl J Med*. 2006;355(23):2427-2443.

Type 2 Diabetes: A Progressive Disease

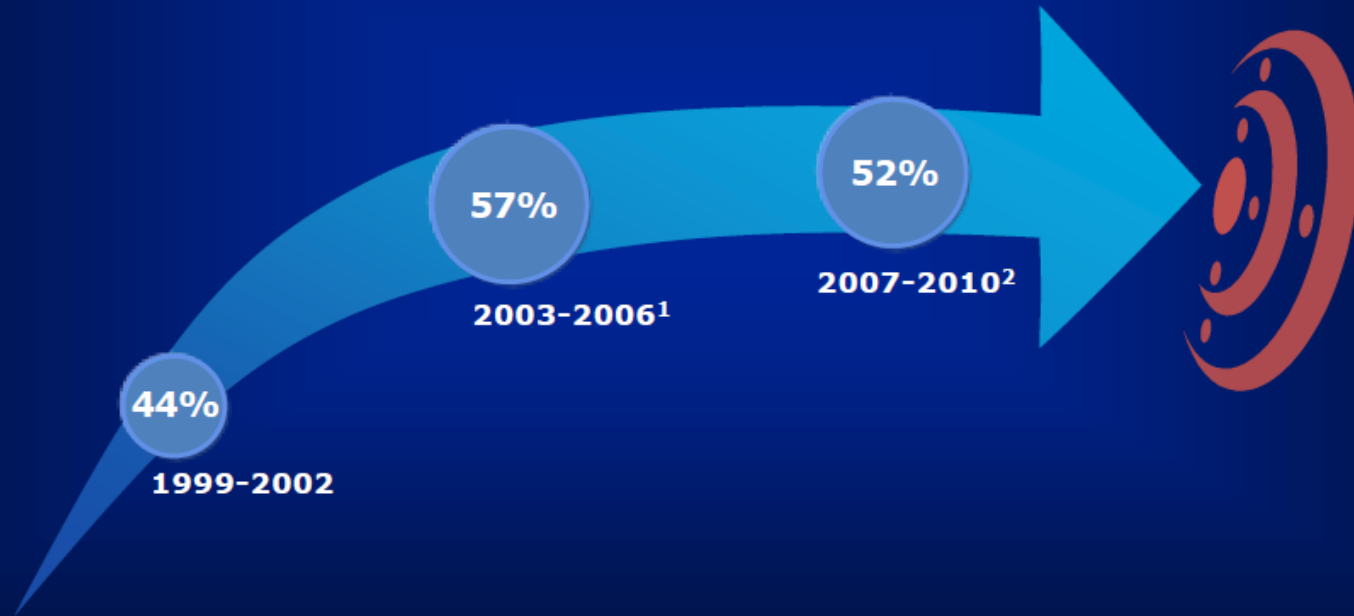


Garber AJ, et al. *Endocr Pract.* 2008;14:933-46.

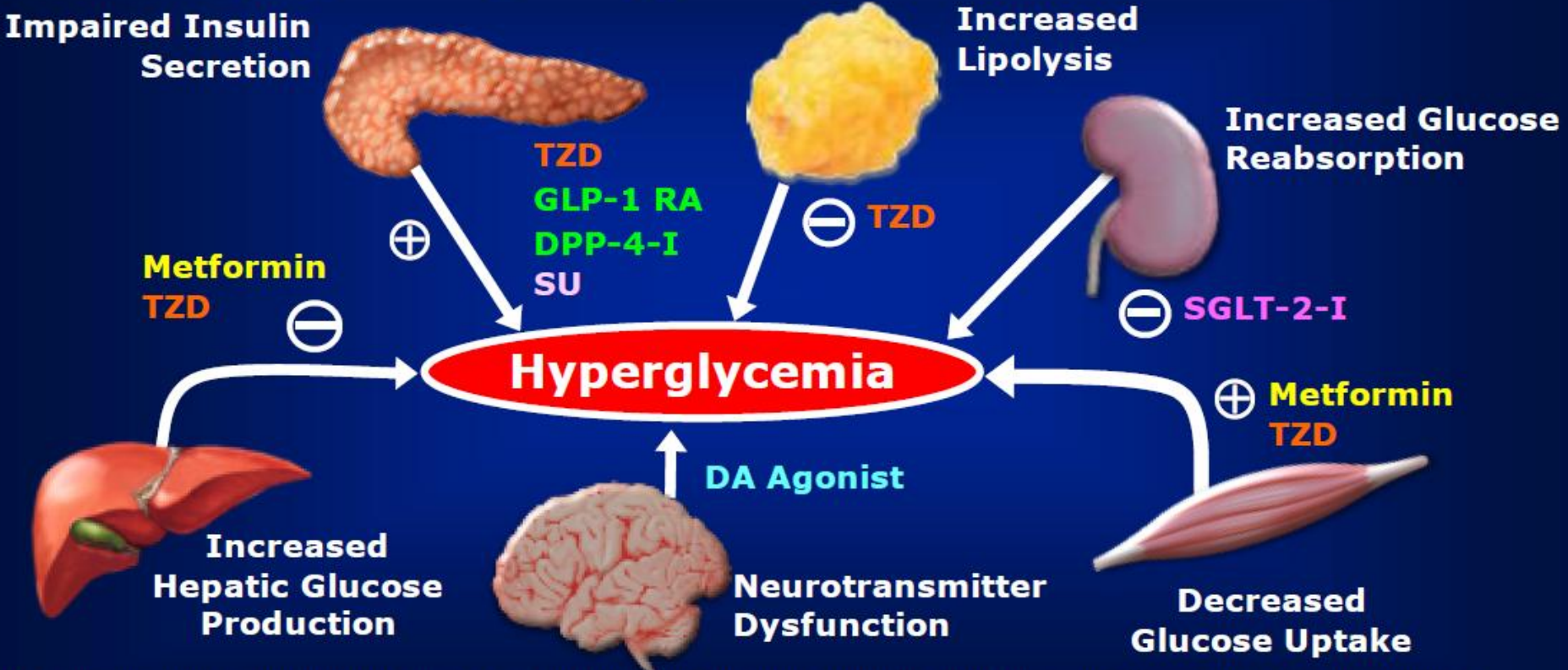
CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

Getting Patients to Goal: Is Progress Slowing Down?

Americans With Diabetes at A1C Target Goal of <7.0%

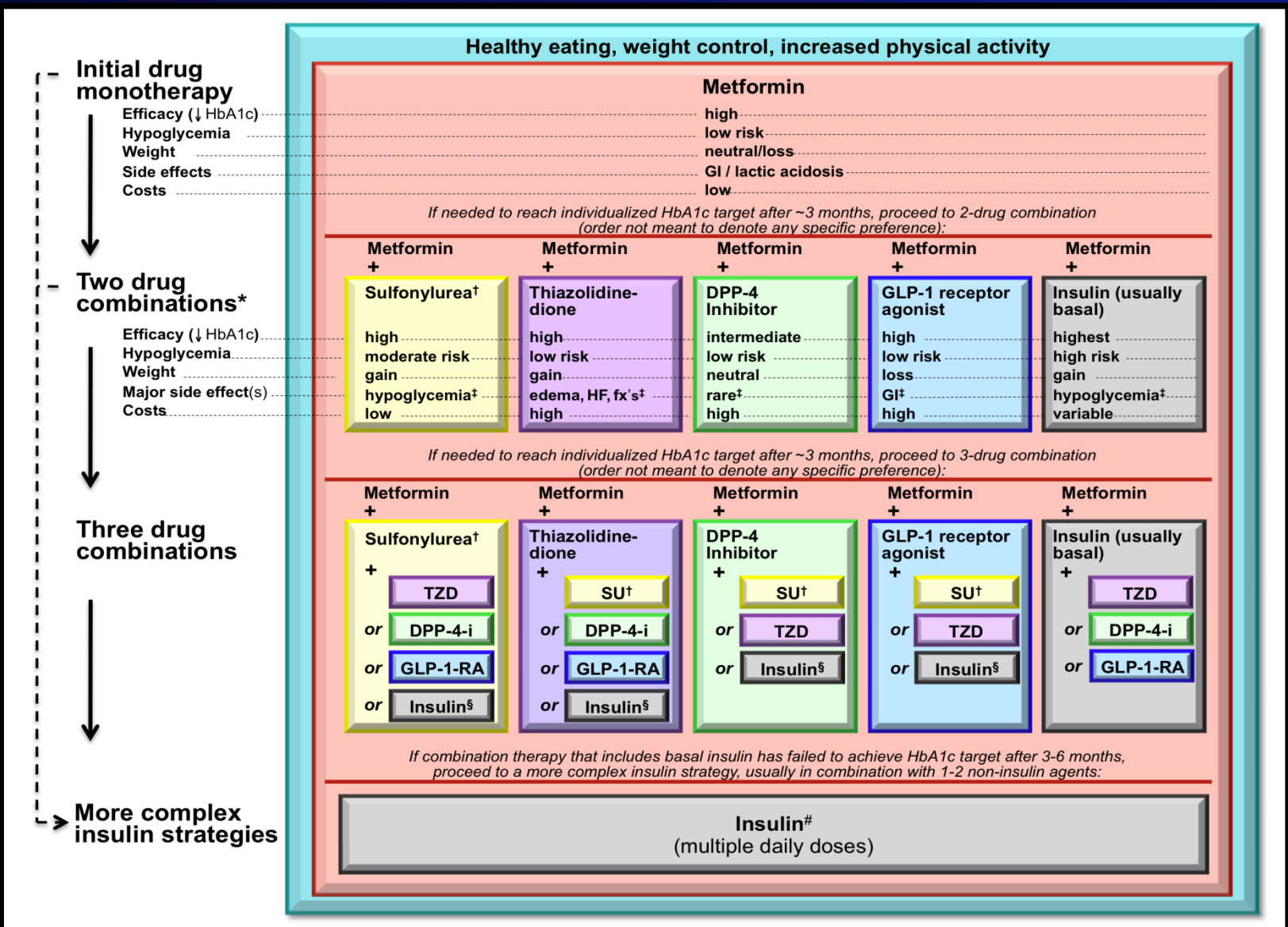


Management of Type 2 Diabetes: A Pathophysiologic Approach



DA=Dopamine; DPP-4-I=DPP-4 Inhibitor; GLP-1 RA=GLP-1 Receptor Agonist; SGLT-2-I=Sodium-Coupled Glucose Transporter-2 Inhibitor; SU=Sulfonylurea; TZD=Thiazolidinedione.
 Reproduced from DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

ADA/EASD T2DM Treatment Algorithm





GLYCEMIC CONTROL ALGORITHM

LIFESTYLE MODIFICATION (Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ DPP4-i
- ✓ AG-i
- ⚠ SGLT-2 **
- ⚠ TZD
- ⚠ SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

- GLP-1 RA ✓
- DPP4-i ✓
- TZD ⚠
- ** SGLT-2 ⚠
- Basal insulin ⚠
- Colesevelam ✓
- Bromocriptine QR ✓
- AG-i ✓
- SU/GLN ⚠

MET or other first-line agent

If not at goal in 3 months proceed to triple therapy

ENTRY A1c > 9.0%

NO SYMPTOMS	SYMPTOMS
DUAL THERAPY OR TRIPLE THERAPY	INSULIN ± OTHER AGENTS

TRIPLE THERAPY*

- GLP-1 RA ✓
- TZD ⚠
- ** SGLT-2 ⚠
- Basal insulin ⚠
- DPP4-i ✓
- Colesevelam ✓
- Bromocriptine QR ✓
- AG-i ✓
- SU/GLN ⚠

2ND LINE AGENT + **MET** or other first-line agent

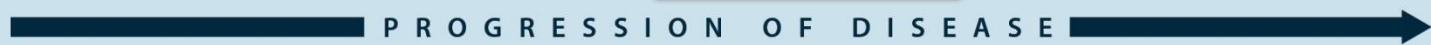
If not at goal in 3 months proceed to or intensify insulin therapy

ADD OR INTENSIFY INSULIN

* Order of medications listed are a suggested hierarchy of usage
 ** Based upon phase 3 clinical trials data

LEGEND

✓ = Few adverse events or possible benefits ⚠ = Use with caution



Patient-Centered Approach in T2DM

- ***Individualize intensiveness of therapy***
 - ***How much to decrease HbA1c***
 - ***How aggressive to be to achieve glycemic goal?***
- ***Individualize treatment strategy***
 - ***What factors make one choice better than another?***
 - ***Desired degree of glucose lowering***
 - ***Added benefits***
 - ***Side effects to avoid/contraindications***
- ***Patients' preferences, needs, and values guide all decision-making***

HbA1c = glycated hemoglobin

Source: Inzucchi SE, et. Al. Diabetologia. 2012; 55(6): 1577-1596

Implications for Therapy

- ***Multiple drugs used in combination***
- ***Address multiple pathogenic abnormalities***
- ***Start early to prevent β -cell failure***

***What is the best
therapeutic option?***

Summary

- ***Type 2 Diabetes is a progressive disorder***
- ***β cell failure is the crux of the problem***
- ***Armamentarium for the treatment of Type 2 Diabetes is expanding***
- ***A patient centered approach, taking into account intensity of treatment, strategies, and patient needs is important***
- ***Treatment algorithms based on known pathophysiological defects has a higher probability of achieving durable glycemic control***

Thank You