Pathophysiology and Epidemiology of Type 2 Diabetes

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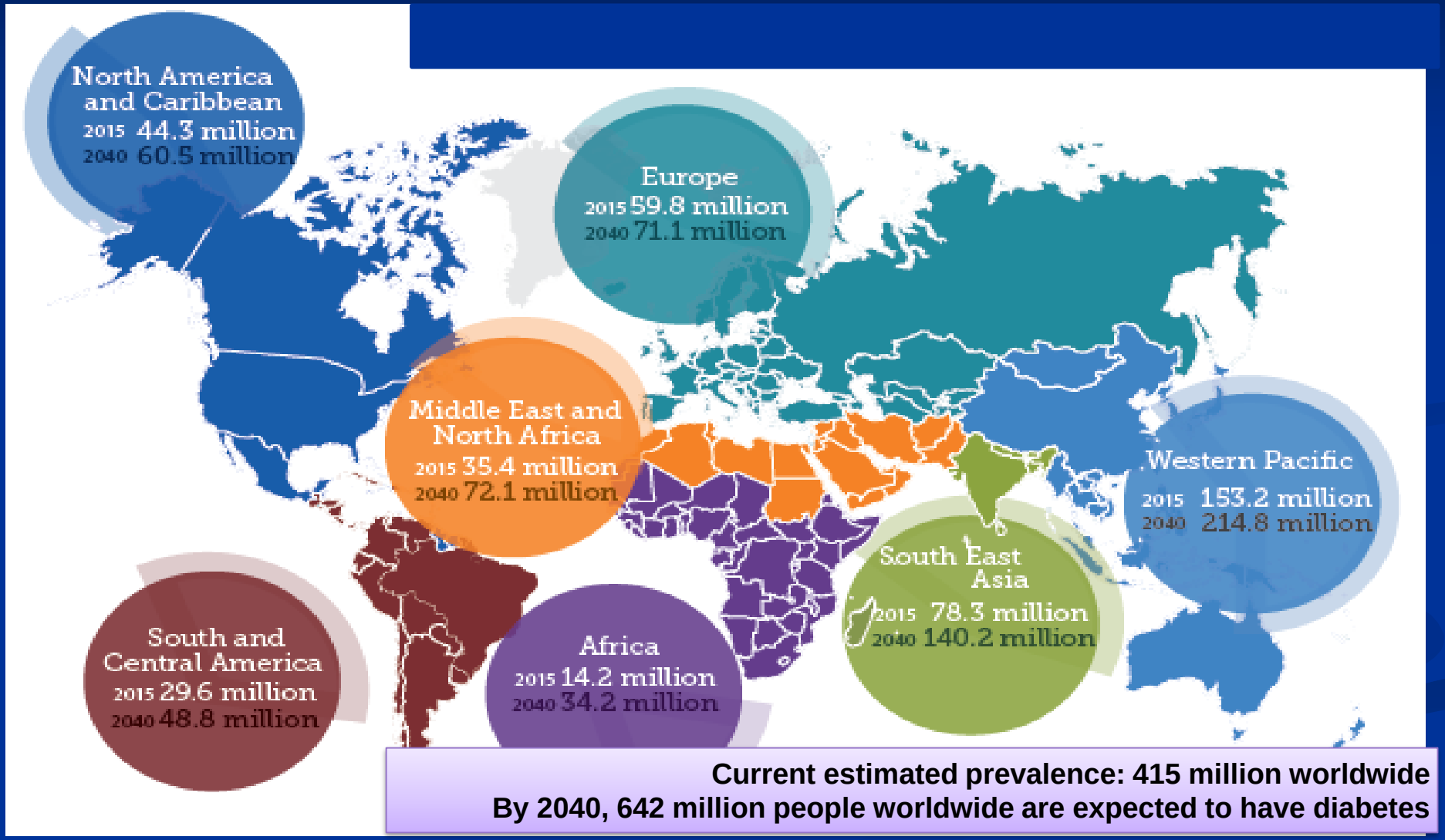
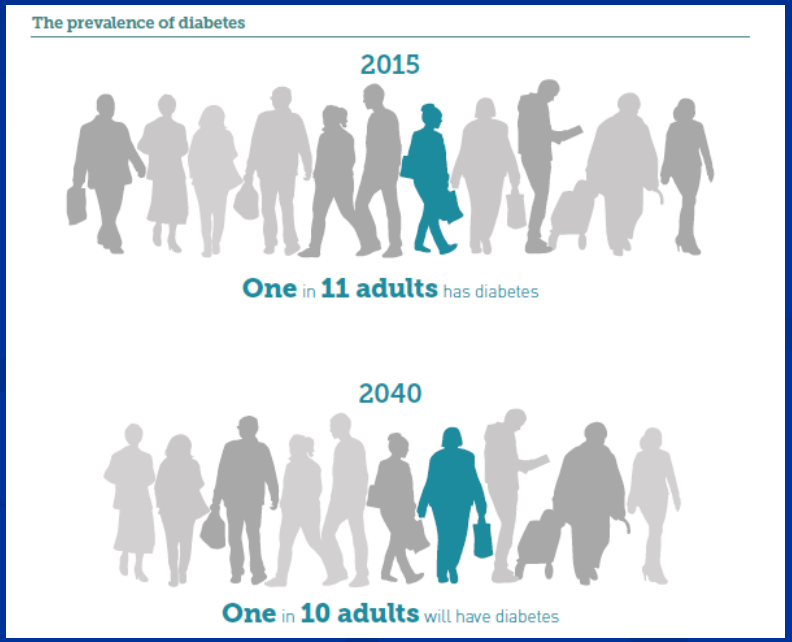
Worldwide Prevalence of Diabetes



Current estimated prevalence: 415 million worldwide
By 2040, 642 million people worldwide are expected to have diabetes

IDF. Diabetes Atlas Update 2015. Available at: http://www.idf.org/sites/default/files/Atlas7e-poster.pdf.

Global Impact: Update

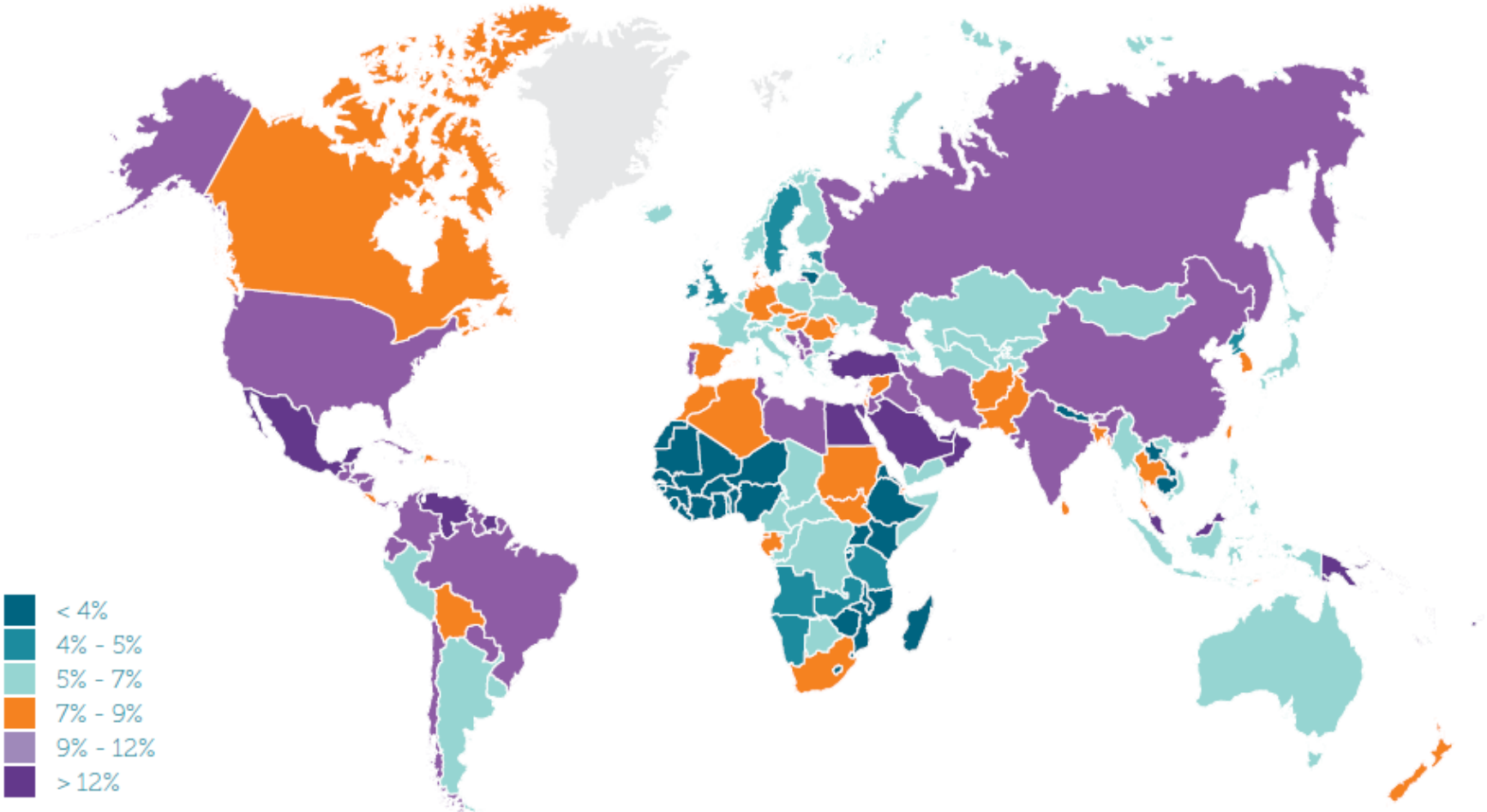


International Diabetes Federation. *IDF Diabetes Atlas, 7th edn.* Vancouver, Canada: International Diabetes Federation, 2015.

International Diabetes Federation

Prevalence of Diabetes in Adults

Map 3.1 Estimated age-adjusted prevalence of diabetes in adults (20-79), 2015



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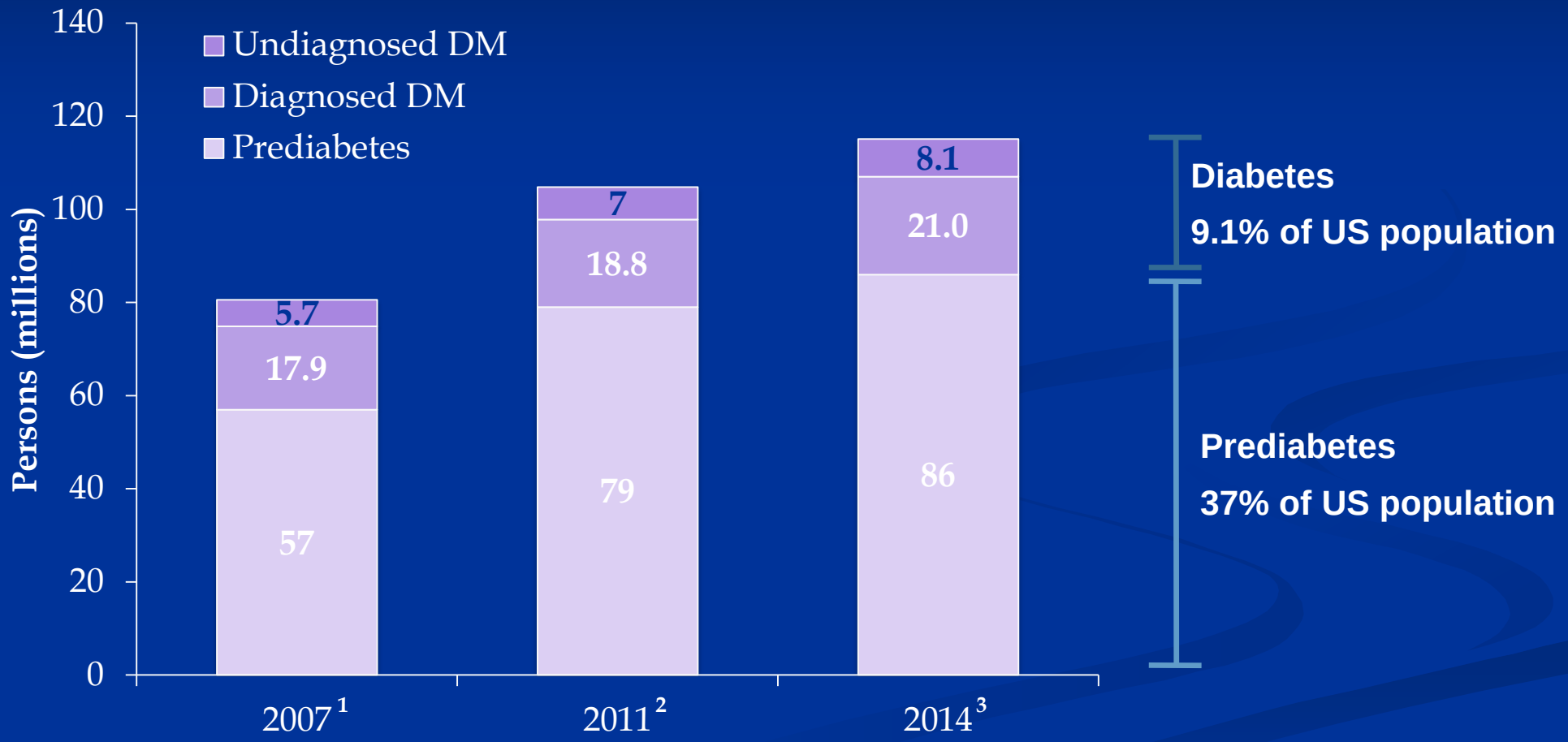
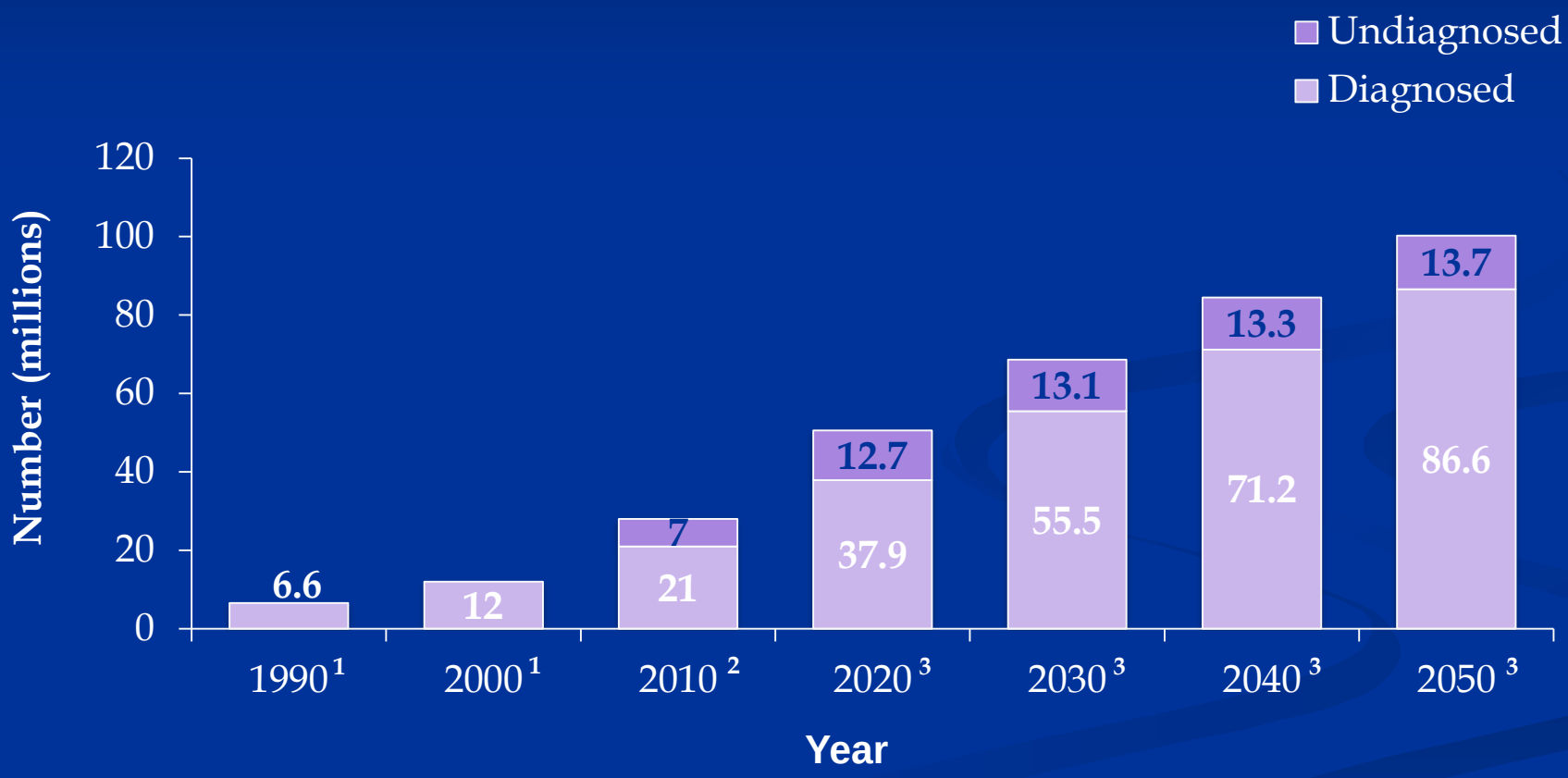
Prevalence of Diabetes and Prediabetes in the United States



1. CDC. National diabetes fact sheet, 2008. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2008.pdf.
2. CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.
3. CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

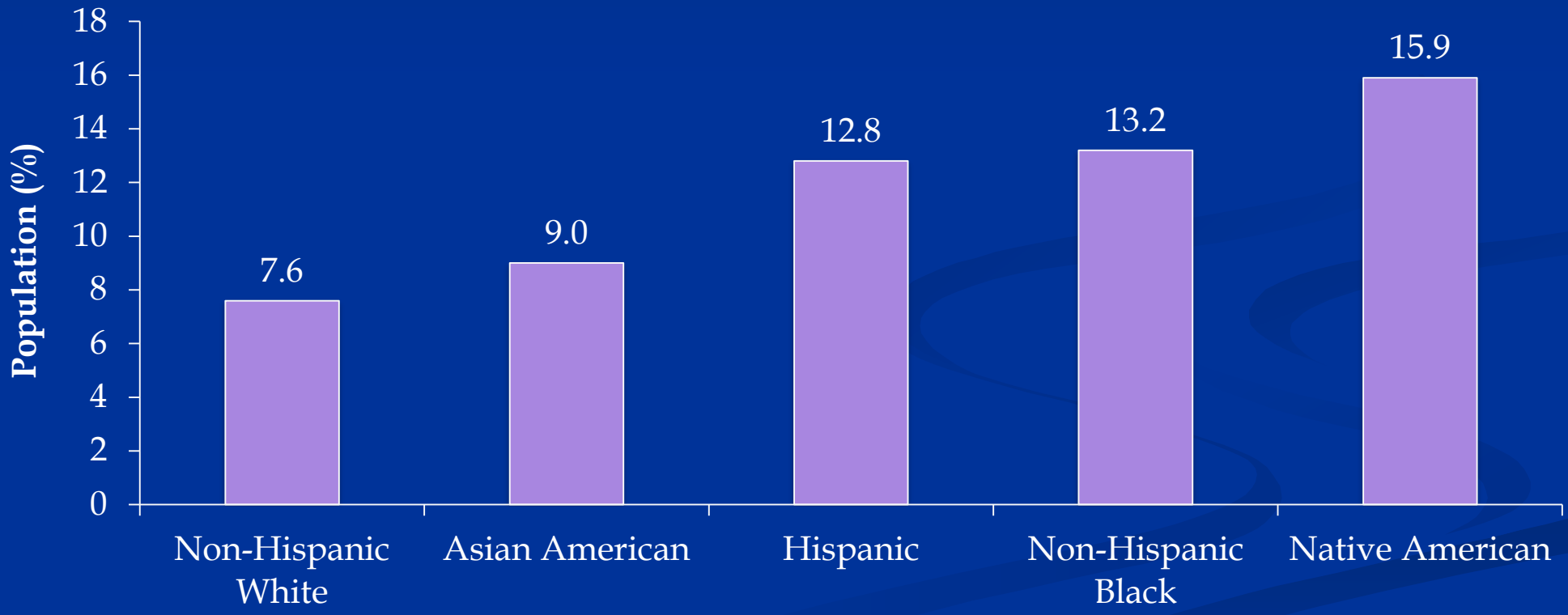
Projected Prevalence of Diabetes in the United States: 1990 to 2050



1. National Diabetes Surveillance System. http://www.cdc.gov/diabetes/statistics/prev/national/figpersons.htm. 2. CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. 3. Boyle JP, et al. *Popul Health Metr*. 2010 Oct 22;8:29.

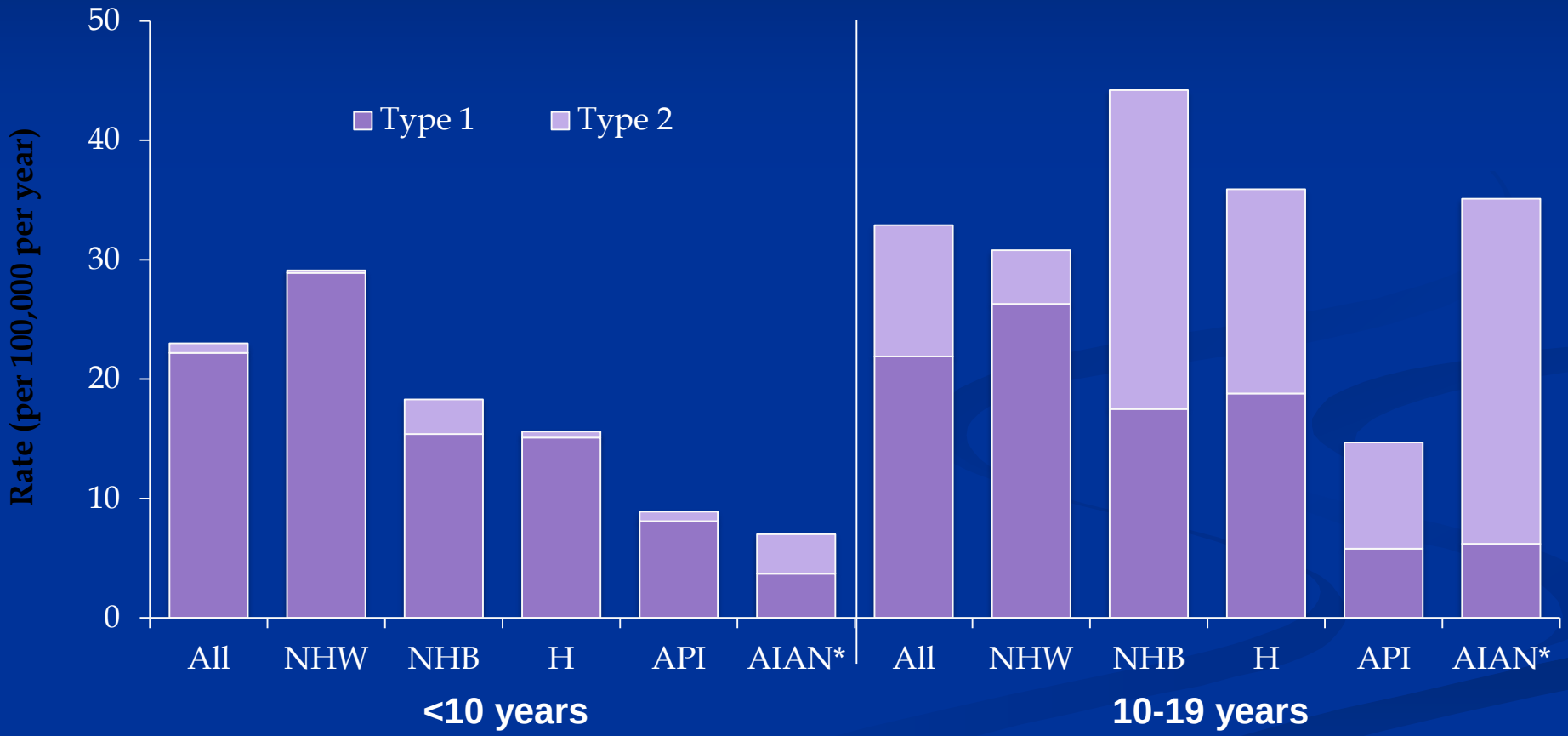
Prevalence of Diagnosed Diabetes in Different US Ethnic and Racial Groups

US Adults ≥20 Years of Age



CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

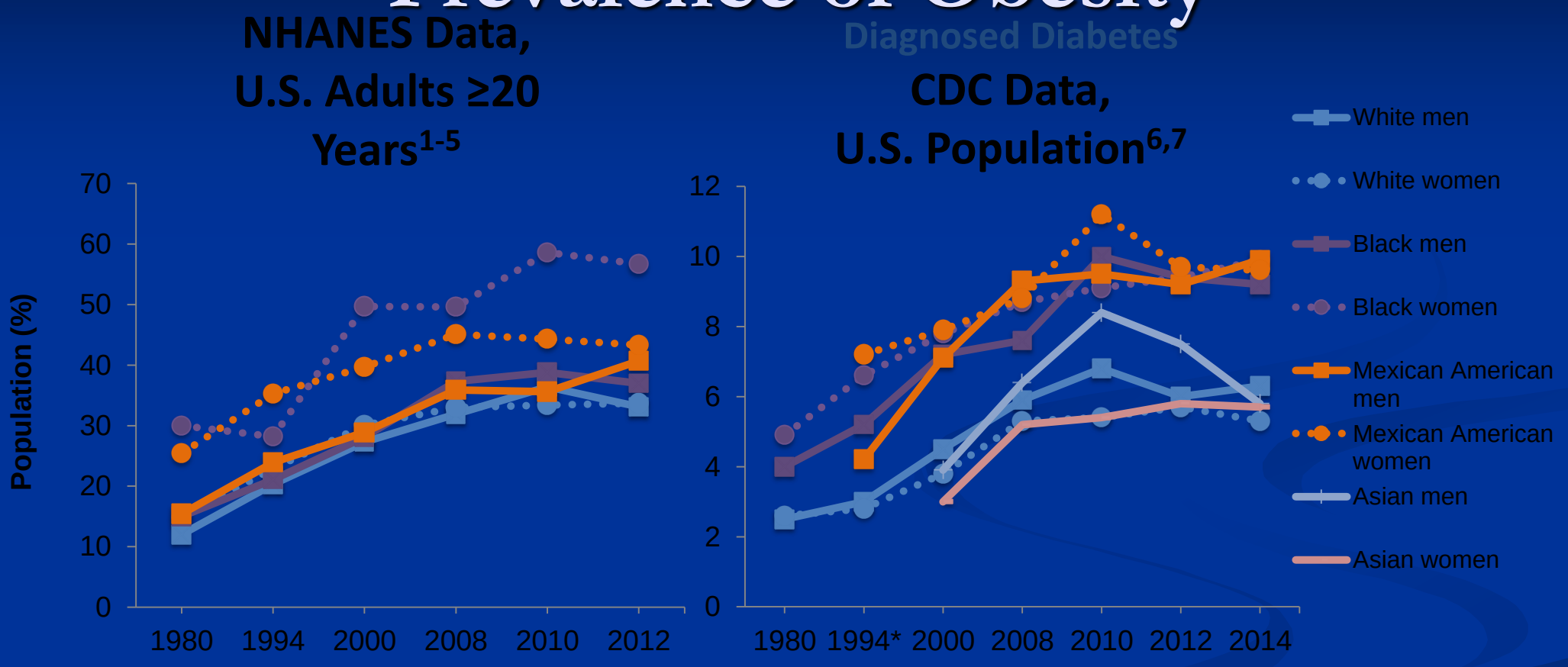
Annual Incidence of Diabetes in US Children and Adolescents



AI, American Indians; API, Asians/Pacific Islanders; H, Hispanics; non-Hispanic blacks; NHW, non-Hispanic whites; NHB.

CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

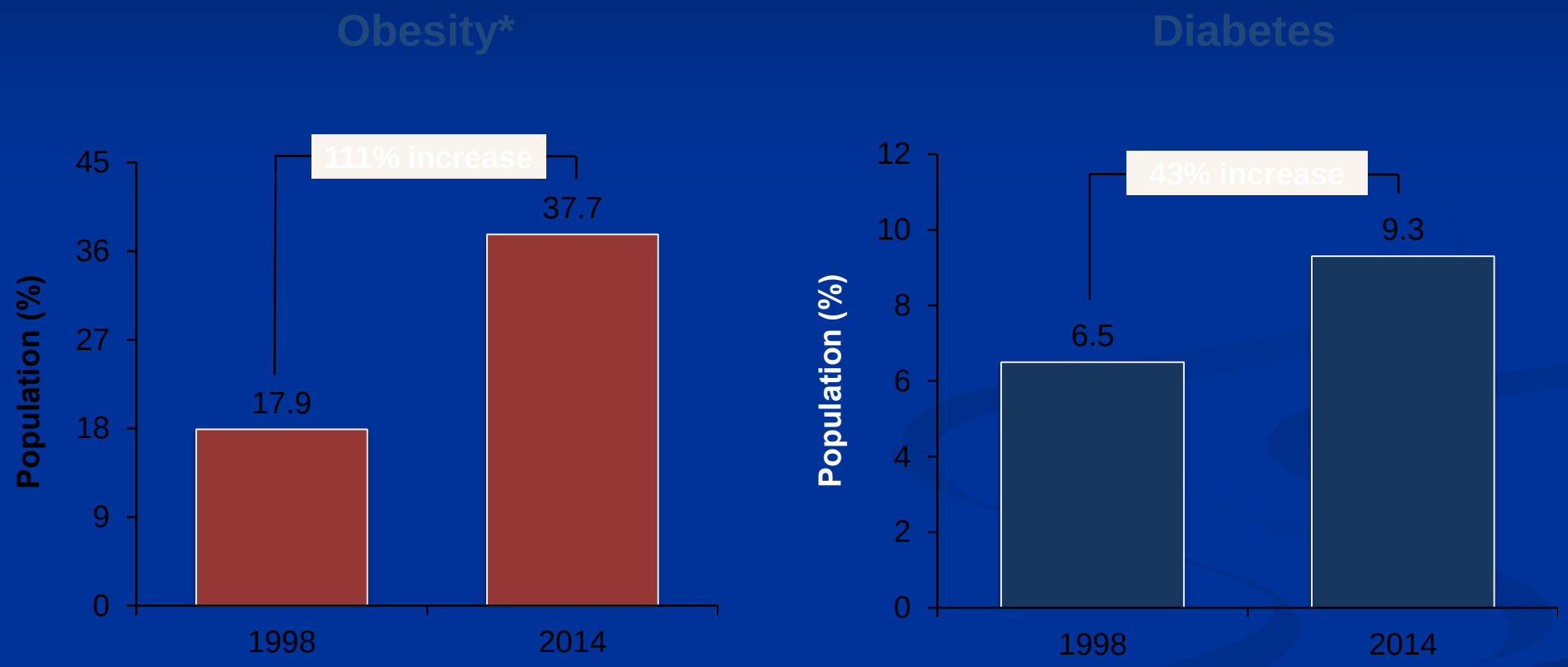
T2D Prevalence Parallels Prevalence of Obesity



BMI, body mass index (in kg/m²); CDC, Centers for Disease Control and Prevention; NHANES, National Health and Nutrition Examination Survey (x-axis lists last year of each survey).
*NHANES 1994 data.

1. Flegal KM, et al. *Int J Obes Relat Metab Disord*. 1998;22:39-47. 2. Flegal KM, et al. *JAMA*. 2002 ;288:1723-1727. 3. Flegal KM, et al. *JAMA*. 2010;303:235-241. 4. Flegal KM, et al. *JAMA*. 2012;307:491-497. 5. Ogden CL, et al. *JAMA*. 2014;311:806-814. 6. Harris MI, et al. *Diabetes Care*. 1998;21:518-524. 7. CDC. Diabetes data & trends. Available at: https://www.cdc.gov/diabetes/statistics/prev/national/figraceethsex.htm and http://www.cdc.gov/diabetes/statistics/prev/national/fighispanicthsex.htm.

Increase in Diabetes Parallels the Increase in Obesity in the United States



*BMI ≥30 kg/m^2.

CDC. National diabetes statistics report, 2014. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2014. Mokdad AH, et al. *JAMA*. 1999;282:1519-1522; Mokdad AH, et al. *Diabetes Care*. 2000;23:1278-1283; Flegal KM, et al. *JAMA*. 2016;315:2284-2291.

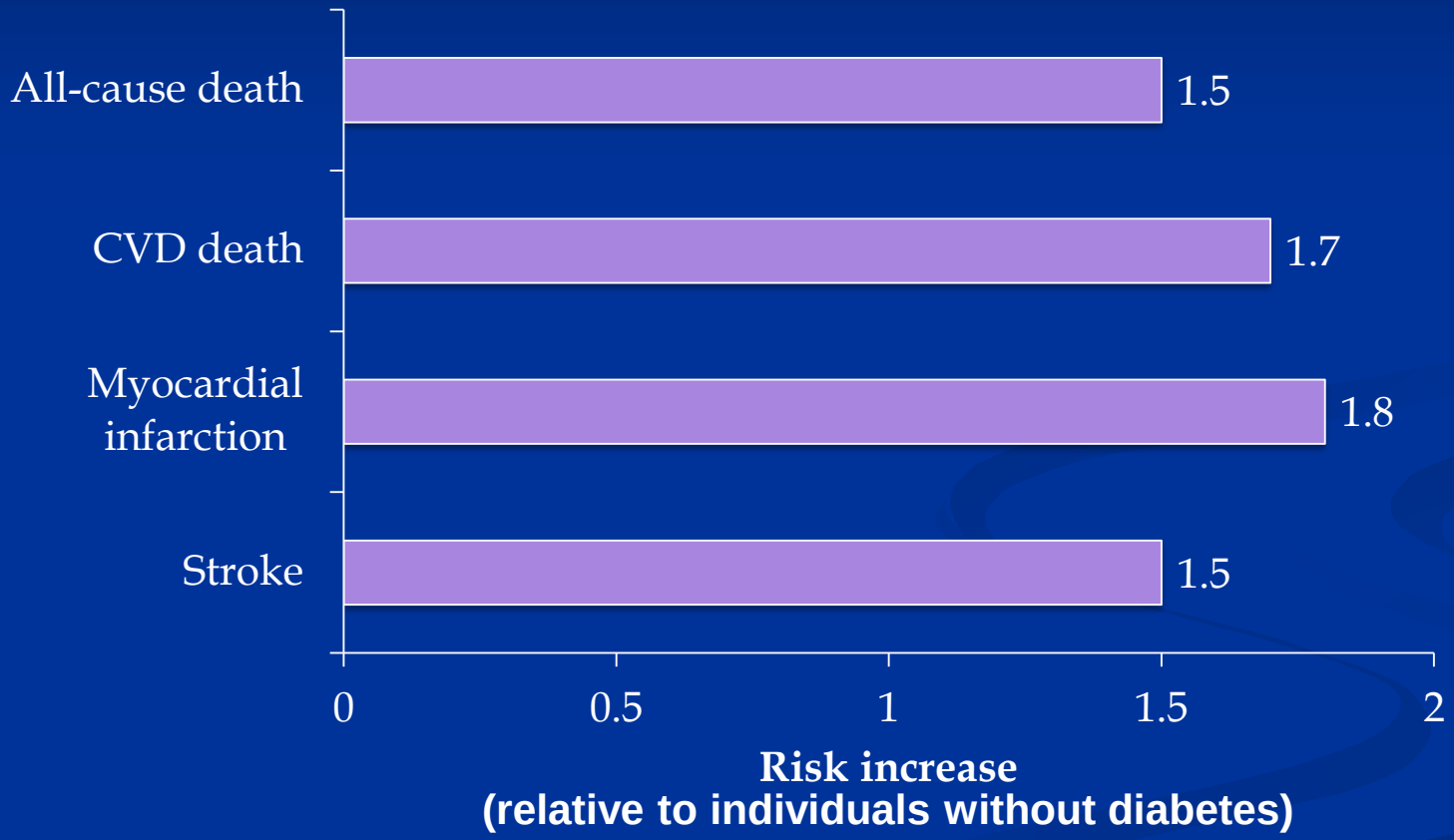
Diabetes Morbidity and Mortality

- 7th leading cause of death in US
- Leading cause of blindness
- Most frequent cause of kidney failure
- ~60% of nontraumatic lower limb amputations occur in people with diabetes

- Diabetes also
  - Doubles the risk of periodontal disease
  - Doubles the risk of developing depression
    - Depression increases T2D risk by 60%
  - Increases patients' susceptibility to acute illness (eg, pneumonia and influenza)
    - Worsens the prognosis of patients with acute illnesses

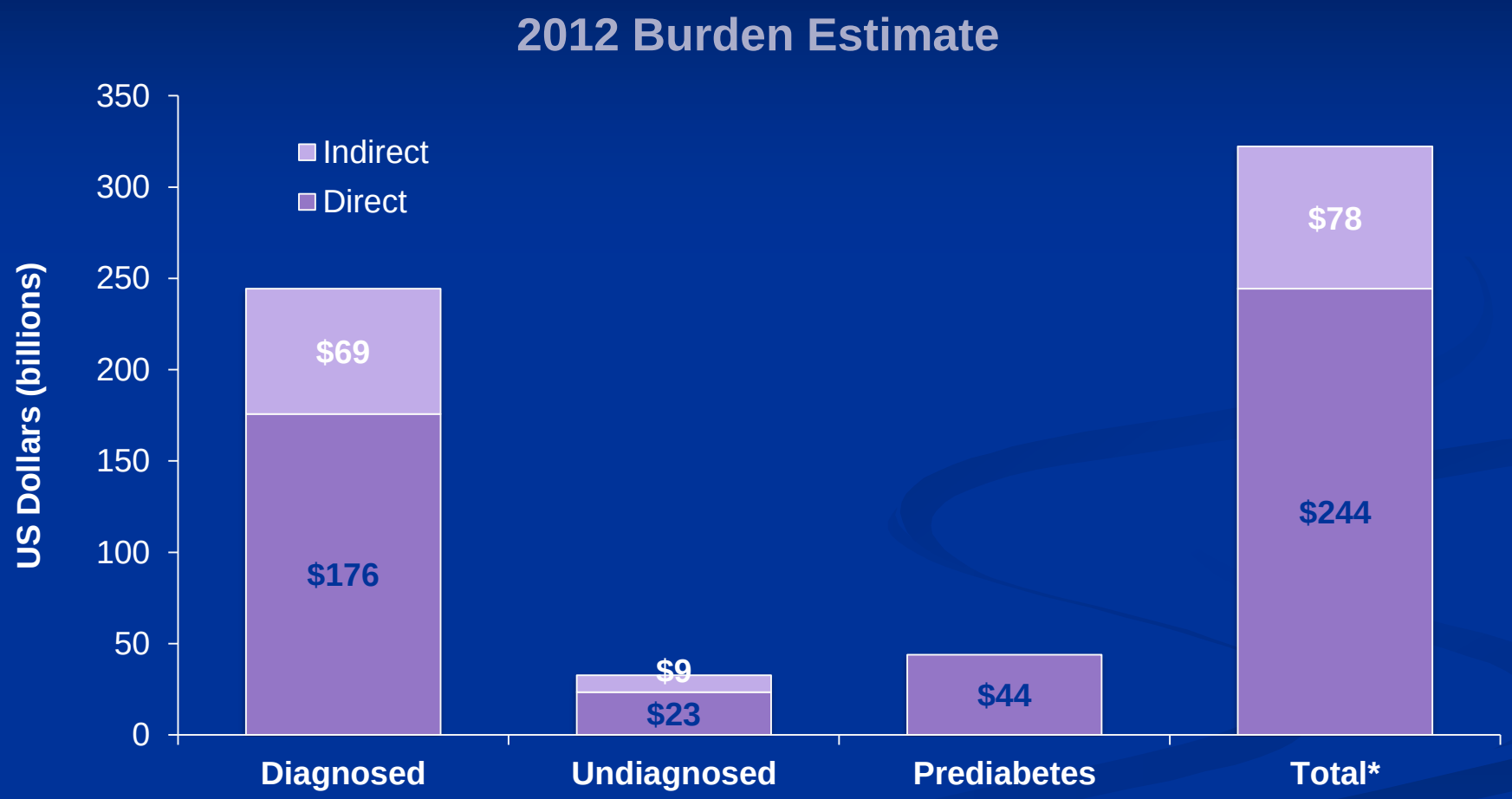
CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
CDC. National diabetes fact sheet, 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

Diabetes and Morbidity and Mortality



CDC. National diabetes statistics report, 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf

Costs of Diabetes

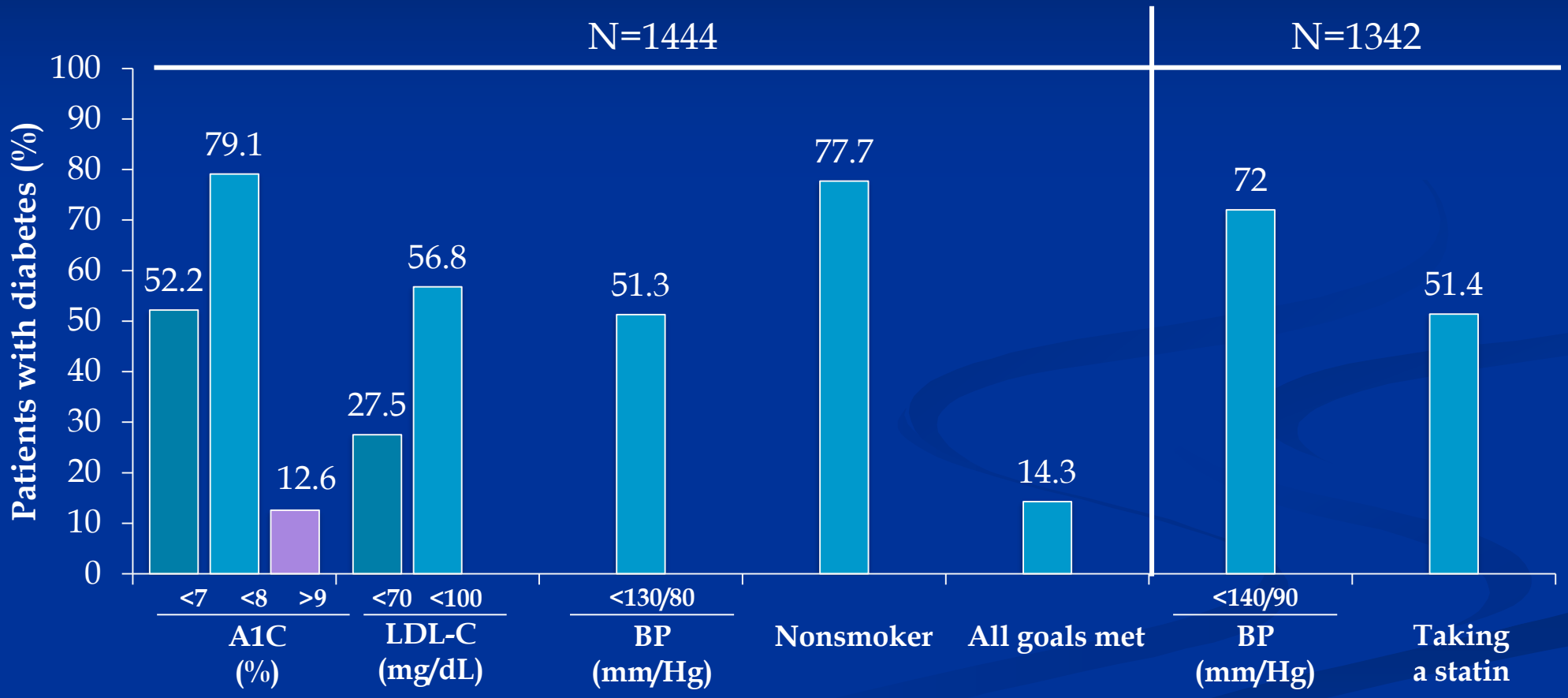


*Includes $1.3 billion in costs from gestational diabetes.

Dall TM, et al. *Diabetes Care*. 2014;37:3172-3179.

Goal Achievement in Diabetes

NHANES 2007-2010*



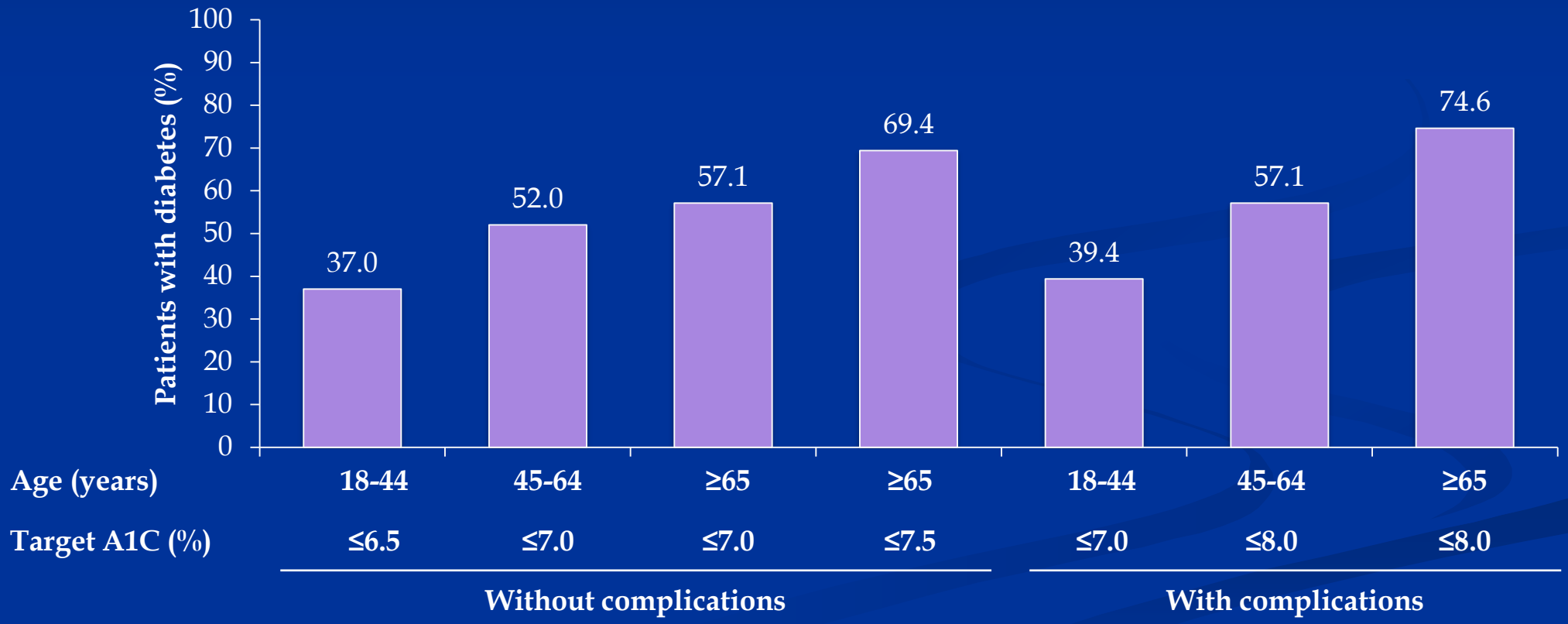
*Data from separate studies.

BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey.

Ali MK, et al. *N Engl J Med*. 2013;368:1613-1624. Stark Casagrande S, et al. *Diabetes Care*. 2013;36:2271-2279.

A1C Achievement by Individualized Target

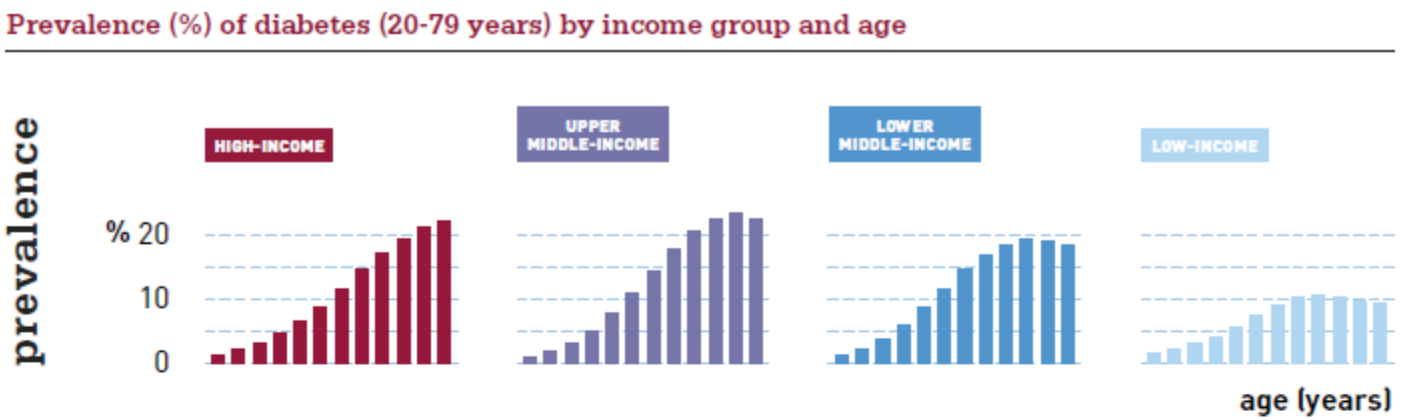
NHANES 2007-2010 (N=1444)



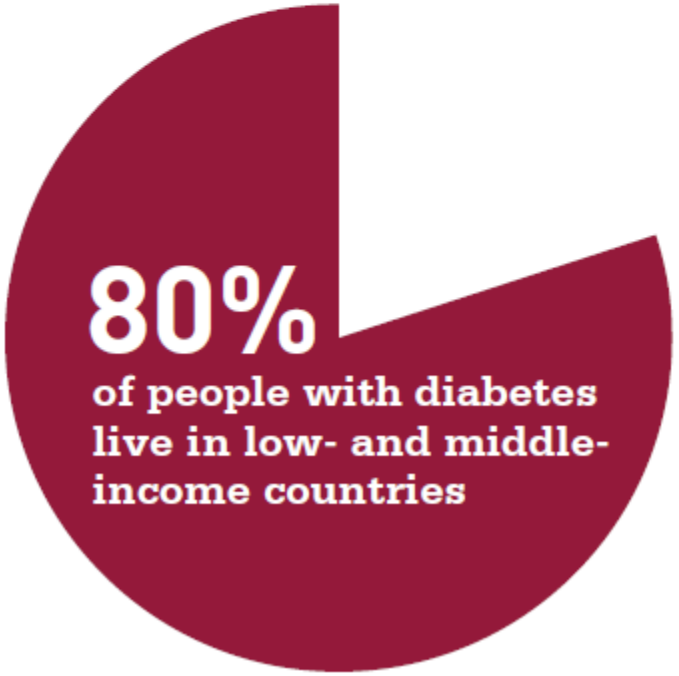
NHANES, National Health and Nutrition Examination Survey.

Ali MK, et al. *N Engl J Med*. 2013;368:1613-1624.

Prevalence by Age and Income



All nations – **rich and poor** – are suffering the impact of the diabetes epidemic.



International Diabetes Federation

Prevalence of Diabetes in Adults

Table 3.2 IDF regions ranked by age-adjusted prevalence (%) of diabetes (20-79 years), 2015 and 2040

		2015		2040	
		Age-adjusted comparative diabetes prevalence	Raw diabetes prevalence	Age-adjusted comparative diabetes prevalence	Raw diabetes prevalence
1	North America and Caribbean	11.5% (9.5-13.0%)	12.9% (10.8-14.5%)	12.0% (9.5-13.7%)	14.7% (11.8-16.7%)
2	Middle East and North Africa	10.7% (7.4-14.2%)	9.1% (6.3-12.2%)	11.1% (7.7-14.9%)	11.4% (7.8-15.1%)
3	South and Central America	9.6% (8.2-11.5%)	9.4% (8.0-11.3%)	9.7% (8.2-11.7%)	11.9% (10.1-14.3%)
4	Western Pacific	8.8% (7.7-10.8%)	9.3% (8.2-11.4%)	9.0% (8.0-11.2%)	11.9% (10.6-14.3%)
5	South-East Asia	8.8% (7.3-10.8%)	8.5% (6.8-10.8%)	9.1% (7.3-11.6%)	10.7% (8.5-13.7%)
6	Europe	7.3% (5.5-10.9%)	9.1% (6.8-13.0%)	7.6% (5.7-11.2%)	10.7% (8.2-14.9%)
7	Africa	3.8% (2.6-7.9%)	3.2% (2.1-6.7%)	4.2% (2.9-8.4%)	3.7% (2.6-7.3%)

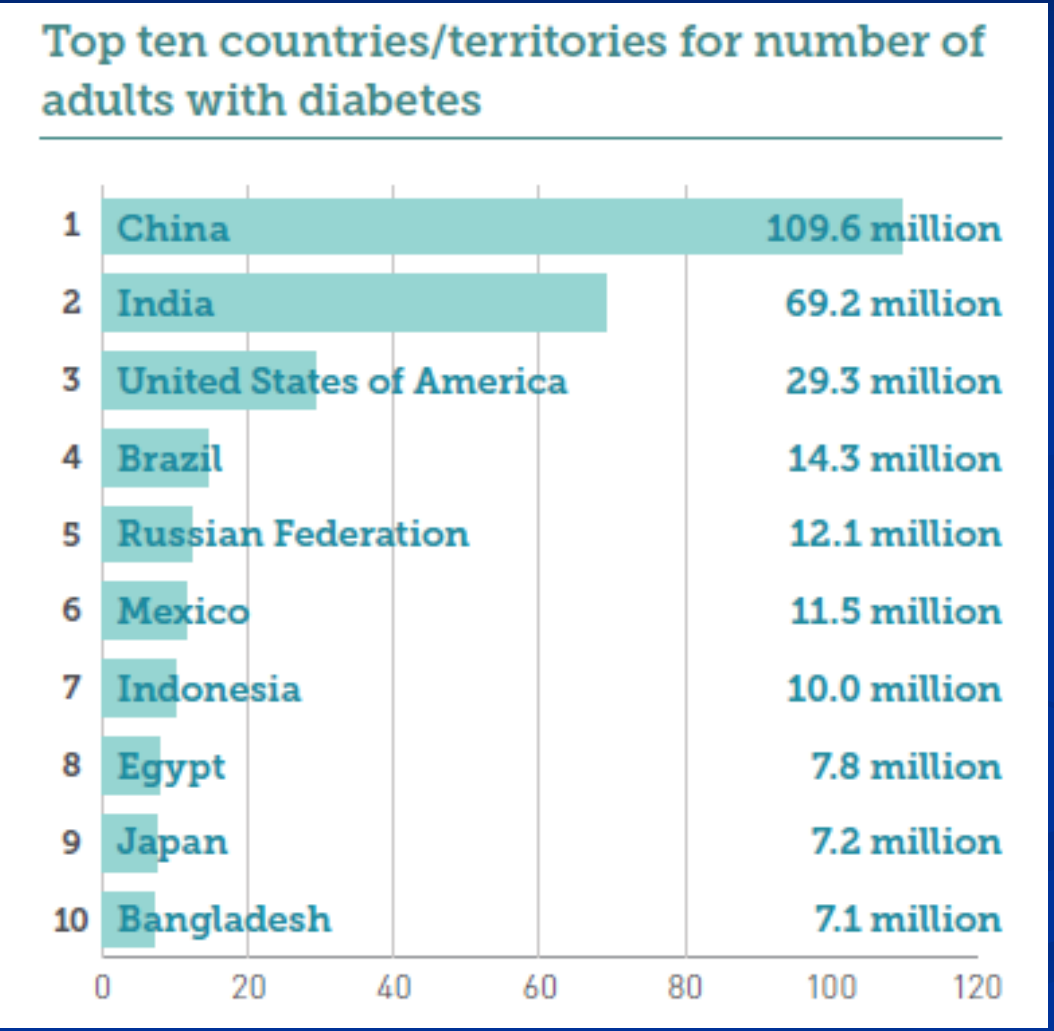
Table 3.1 *IDF Diabetes Atlas* global estimates, 2015 and 2040

	2015	2040
Total world population	7.3 billion	9.0 billion
Adult population (20-79 years)	4.72 billion	6.16 billion
Child population (0-14 years)	1.92 billion	-
Diabetes (20-79 years)		
Global prevalence	8.8% (7.2-11.4%)	10.4% (8.5-13.5%)
Number of people with diabetes	415 million (340-536 million)	642 million (521-829 million)
Number of deaths due to diabetes	5.0 million	-
Health expenditure due to diabetes (20-79 years)		
Total health expenditure, R=2* 2015 USD	673 billion	802 billion
Hyperglycaemia in pregnancy (20-49 years)		
Proportion of live births affected	16.2%	-
Number of live births affected	20.9 million	-
Impaired glucose tolerance (20-79 years)		
Global prevalence	6.7% (4.5-12.1%)	7.8% (5.2-13.9%)
Number of people with impaired glucose tolerance	318 million (212.2-571.6 million)	481 million (317.1-855.7 million)
Type 1 diabetes (0-14 years)		
Number of children with type 1 diabetes	542,000	-
Number of newly diagnosed cases each year	86,000	-

Regional Statistics

- **Africa:** More than 2/3 of people with diabetes are undiagnosed; 52% of deaths due to diabetes are <60 years old
- In the **Middle East and North Africa**, 4/10 adults with diabetes are undiagnosed
- About 1/8 adults in **North America and the Caribbean** has diabetes
- In **Southeast Asia**, 25% of all births are affected by hyperglycemia
- 37% of all adults with diabetes live in the **Western Pacific**
- **Europe** has the highest prevalence of children with **T1DM**

The Top 10 Countries: Numbers of People with Diabetes (in Millions)



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Clinical Presentation of Type 2 Diabetes

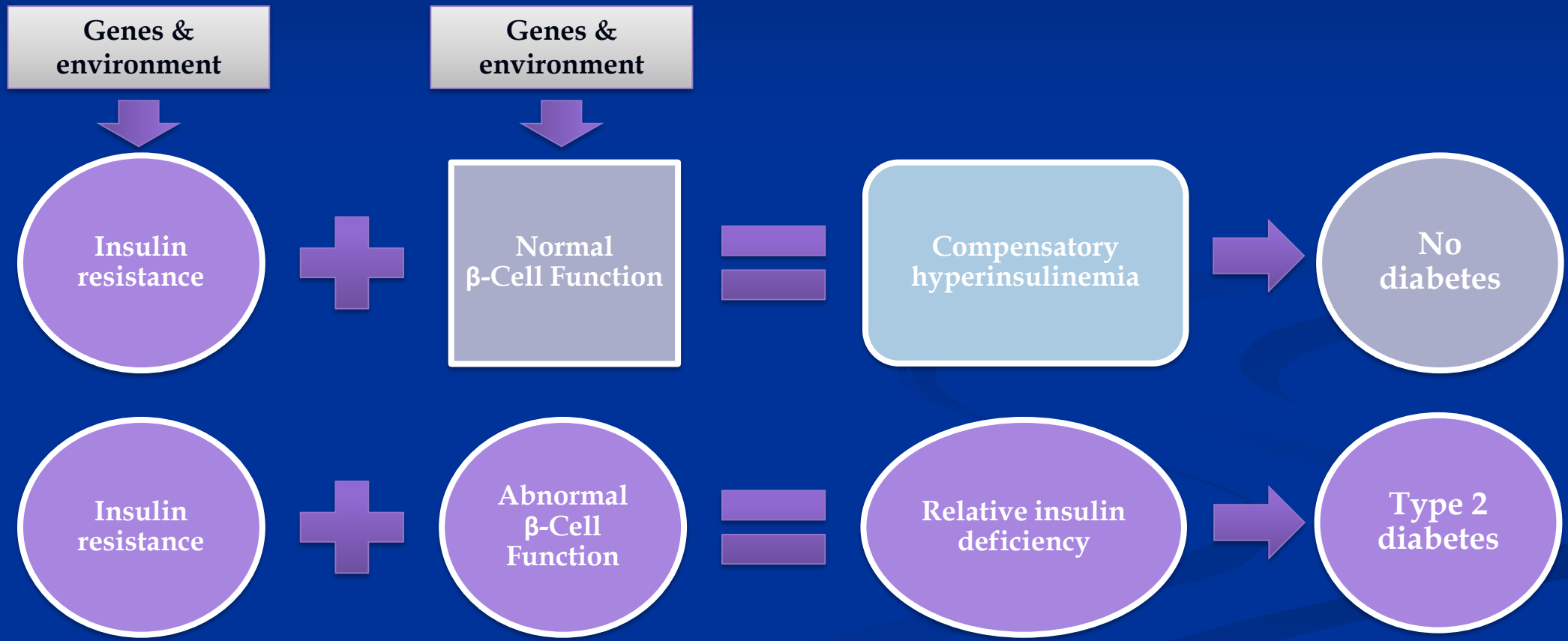
Risk Factors for Prediabetes and Type 2 Diabetes

- Age ≥45 years
- Family history of T2D or cardiovascular disease
- Overweight or obese
- Sedentary lifestyle
- Non-Caucasian ancestry
- Previously identified IGT, IFG, and/or metabolic syndrome
- PCOS, acanthosis nigricans, or NAFLD
- Hypertension (BP >140/90 mmHg)
- Dyslipidemia (HDL-C <35 mg/dL and/or triglycerides >250 mg/dL)
- History of gestational diabetes
- Delivery of baby weighing >4 kg (>9 lb)
- Antipsychotic therapy for schizophrenia or severe bipolar disease
- Chronic glucocorticoid exposure
- Sleep disorders
  - Obstructive sleep apnea
  - Chronic sleep deprivation
  - Night shift work

BP, blood pressure; HCL-C, high density lipoprotein cholesterol; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NAFLD, nonalcoholic fatty liver disease; PCOS, polycystic ovary syndrome; T2D, type 2 diabetes.

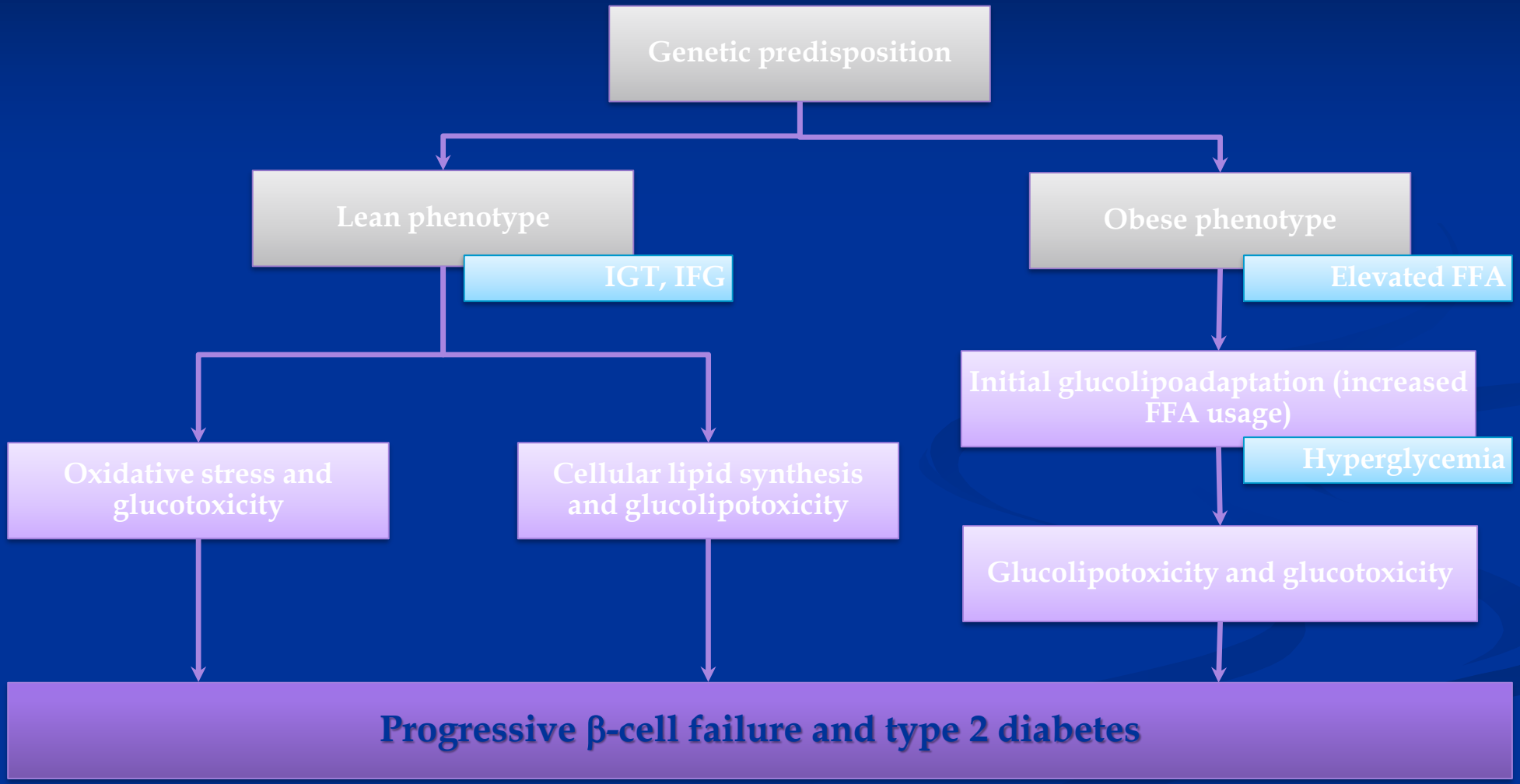
Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

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



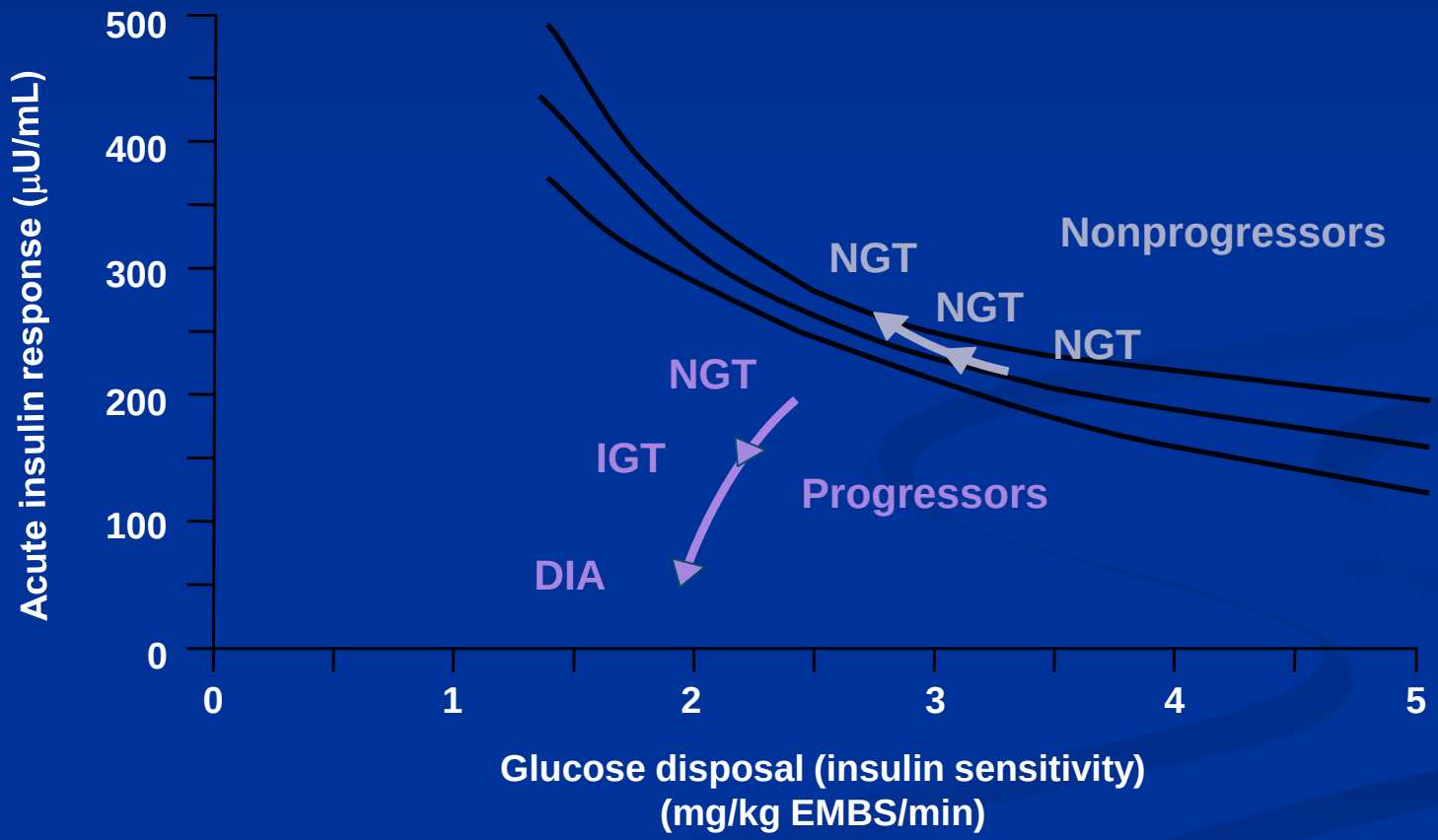
Gerich JE. *Mayo Clin Proc*. 2003;78:447-456.

Etiology of β-cell Dysfunction



Poitout V, Robertson RP. *Endocrine Rev*. 2008;29:351-366.

Progression to Type 2 Diabetes: "Falling Off the Curve"



EMBS, estimated metabolic body size; IGT, impaired glucose tolerance; NGT, normal glucose tolerance.

Weyer C et al. *J Clin Invest*. 1999;104:787-794.

Pathophysiology of Type 2 Diabetes

Organ System	Defect
Major Role	
Pancreatic beta cells	Decreased insulin secretion
Muscle	Inefficient glucose uptake
Liver	Increased endogenous glucose secretion
Contributing Role	
Adipose tissue	Increased FFA production
Digestive tract	Decreased incretin effect
Pancreatic alpha cells	Increased glucagon secretion
Kidney	Increased glucose reabsorption
Nervous system	Neurotransmitter dysfunction

DeFronzo RA. *Diabetes*. 2009;58:773-795

Tissues Involved in T2D Pathophysiology

Organ System	Normal Metabolic Function	Defect in T2D
Major Role		
Pancreatic beta cells	Secrete insulin	Decreased insulin secretion
Muscle	Metabolizes glucose for energy	Inefficient glucose uptake
Liver	Secretes glucose during fasting periods to maintain brain function; main site of gluconeogenesis (glucose production in the body)	Increased endogenous glucose secretion
Contributing Role		
Adipose tissue (fat)	Stores small amounts of glucose for its own use. When fat is broken down, glycerol is released, which is used by the liver to produce glucose	Increased FFA production
Digestive tract	Digests and absorbs carbohydrates and secretes incretin hormones	Decreased incretin effect
Pancreatic alpha cells	Secrete glucagon, which stimulates hepatic glucose production between meals and also helps suppress insulin secretion during fasting periods	Increased glucagon secretion
Kidney	Reabsorbs glucose from renal filtrate to maintain glucose at steady-state levels; also an important site for gluconeogenesis (glucose production)	Increased glucose reabsorption
Brain	Utilizes glucose for brain and nerve function Regulates appetite	Neurotransmitter dysfunction

T2D, type 2 diabetes.

DeFronzo RA. *Diabetes*. 2009;58:773-795

Natural History of Type 2 Diabetes

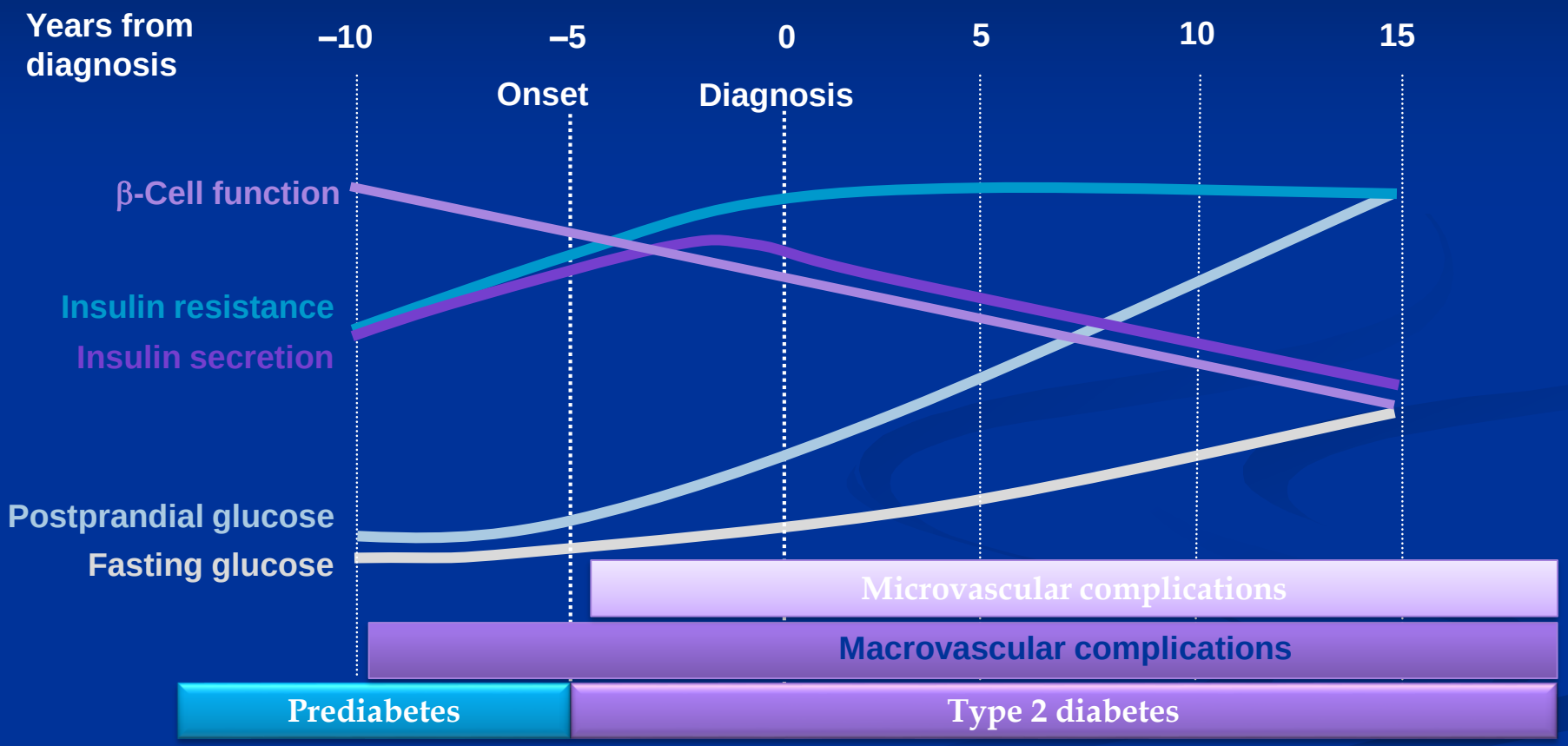
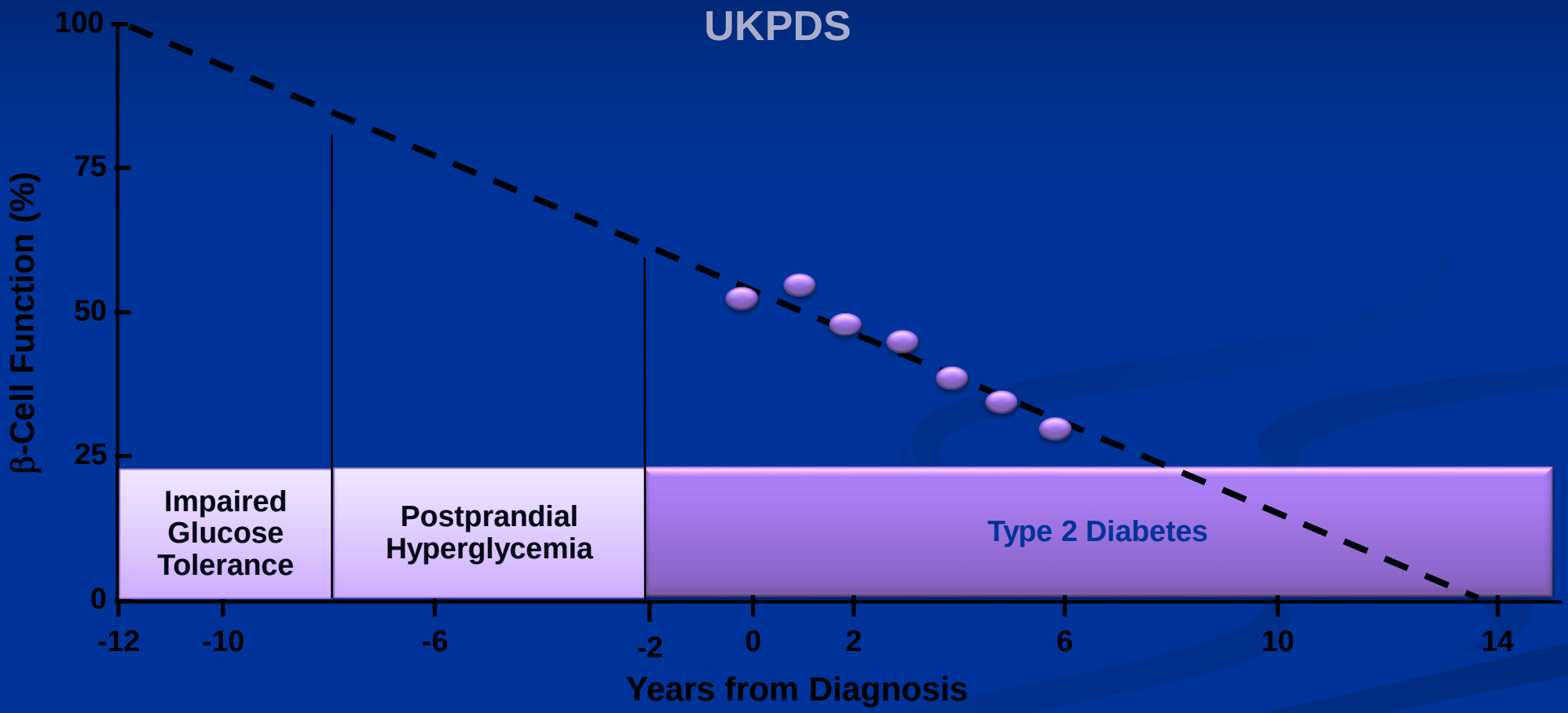


Figure courtesy of CADRE.

Adapted from Holman RR. *Diabetes Res Clin Pract*. 1998;40(suppl):S21-S25; Ramlo-Halsted BA, Edelman SV. *Prim Care*. 1999;26:771-789; Nathan DM. *N Engl J Med*. 2002;347:1342-1349; UKPDS Group. *Diabetes*. 1995;44:1249-1258

β-cell Loss Over Time

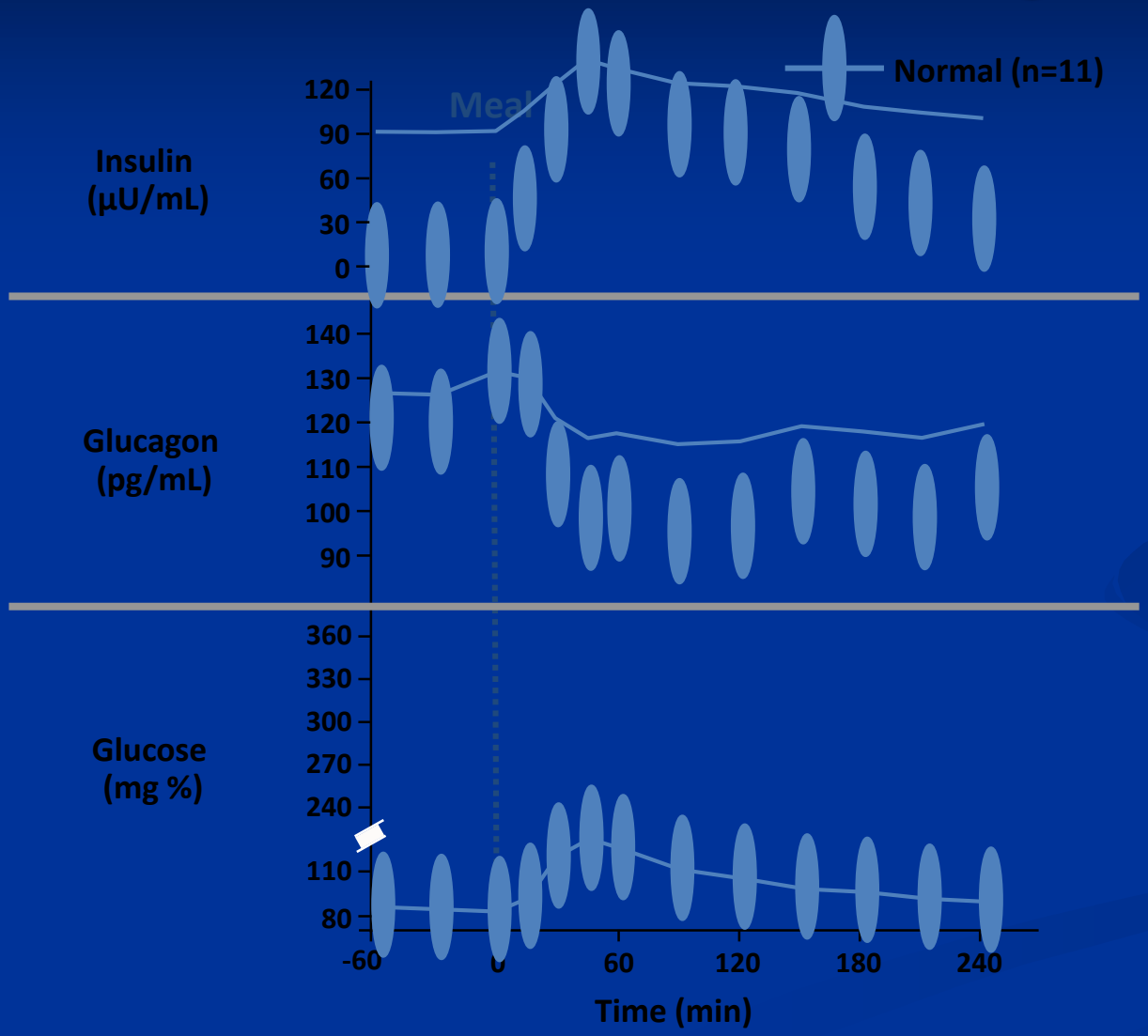


Dashed line = extrapolation based on Homeostasis Model Assessment (HOMA) data.

Data points from obese UKPDS population, determined by HOMA model.

Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl):S21-S25.

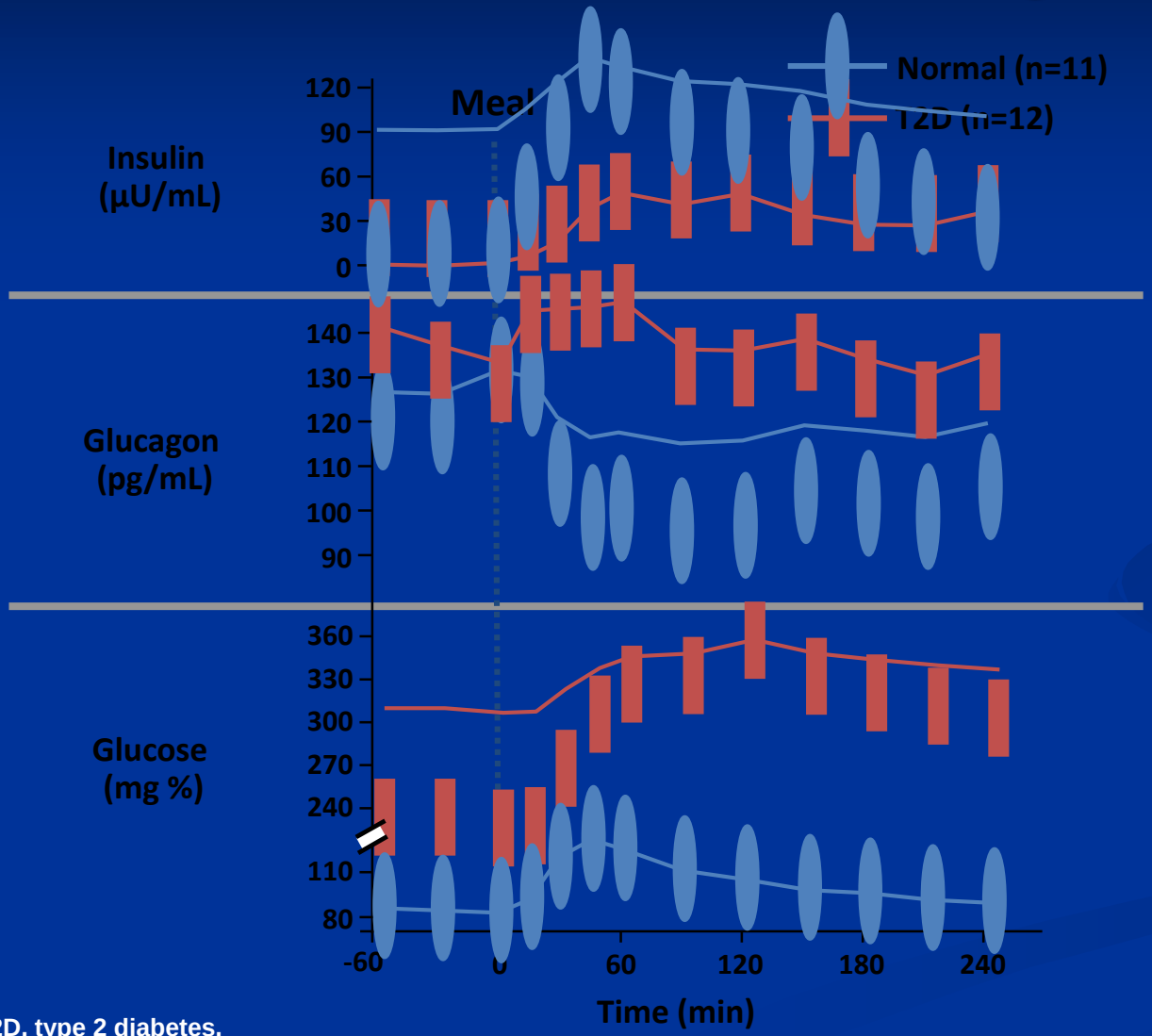
Normal Glucose Homeostasis and Pre- and Postmeal Insulin and Glucagon Dynamics



Premeal	Postmeal
↓ Insulin	↑ Insulin
↑ Glucagon ↑ HGP	↓ Glucagon ↓ HGP
Just enough glucose to meet metabolic needs between meals	Modest postprandial increase with prompt return to fasting levels

Müller WA, et al. *N Engl J Med*. 1970;283:109-115.

Hyperglycemia in Type 2 Diabetes Results from Abnormal Insulin and Glucagon Dynamics

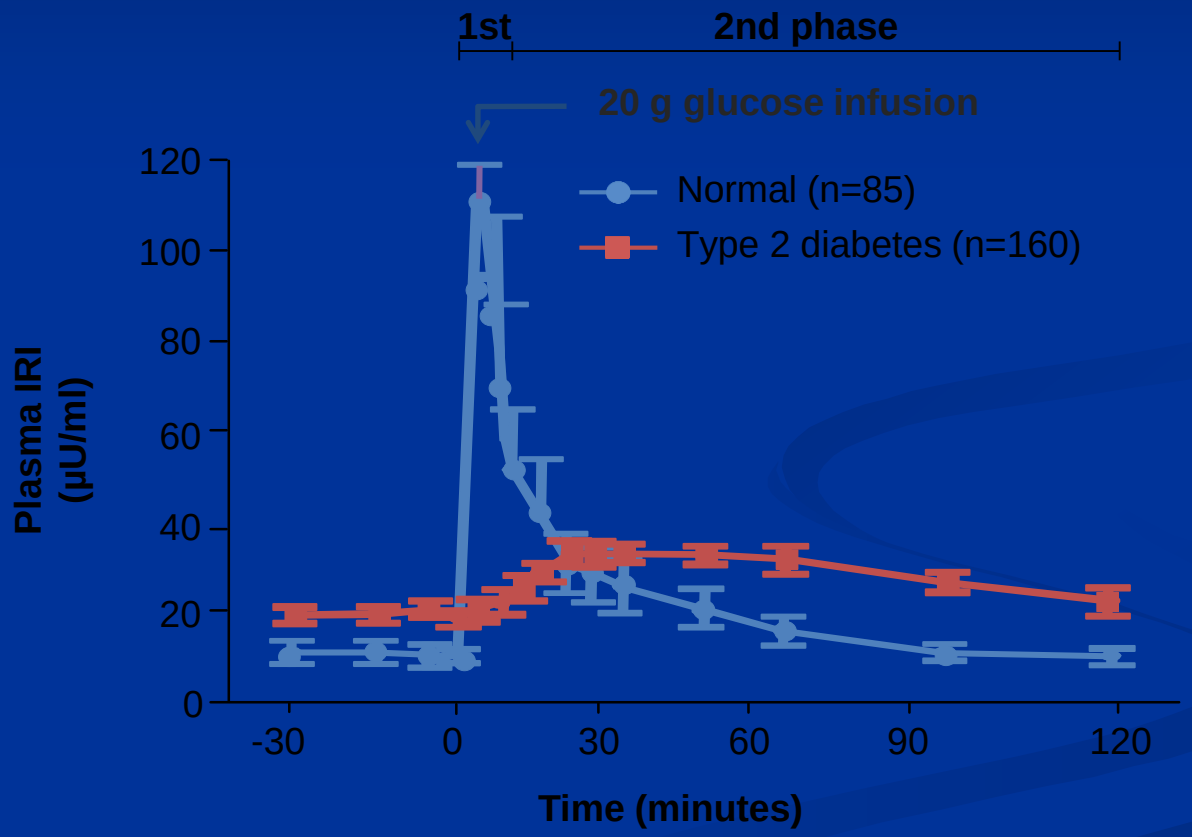


Premeal	Postmeal
↓ Insulin	↓ Insulin
↑ Glucagon ↑ HGP	↑ Glucagon ↑ HGP
↑ FPG	↑↑ PPG

T2D, type 2 diabetes.

Müller WA, et al. *N Engl J Med*. 1970;283:109-115.

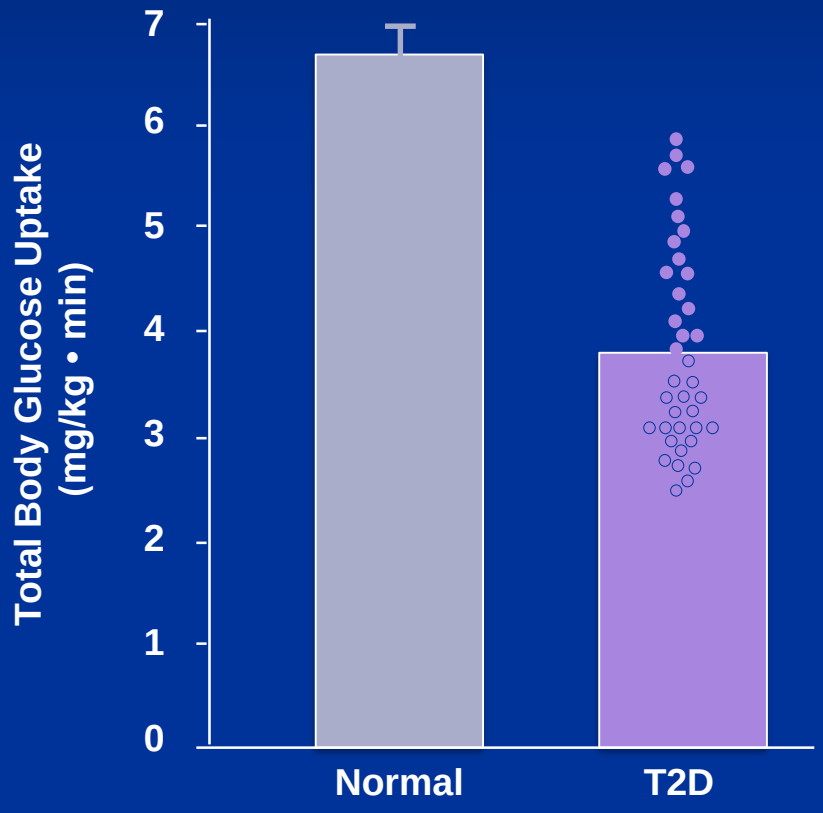
Acute Insulin Response Is Reduced in Type 2 Diabetes

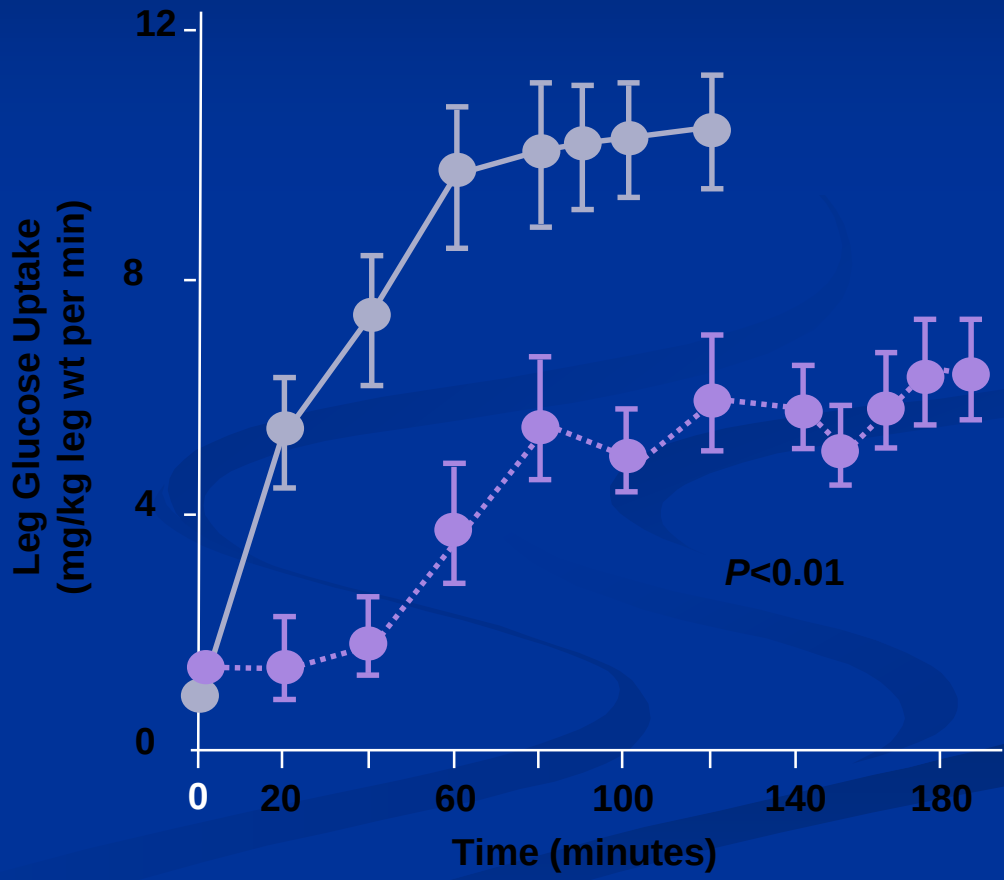


IRI, immunoreactive insulin.

Pfeifer MA, et al. *Am J Med*. 1981;70:579-588.

Defective Insulin Action in Type 2 Diabetes

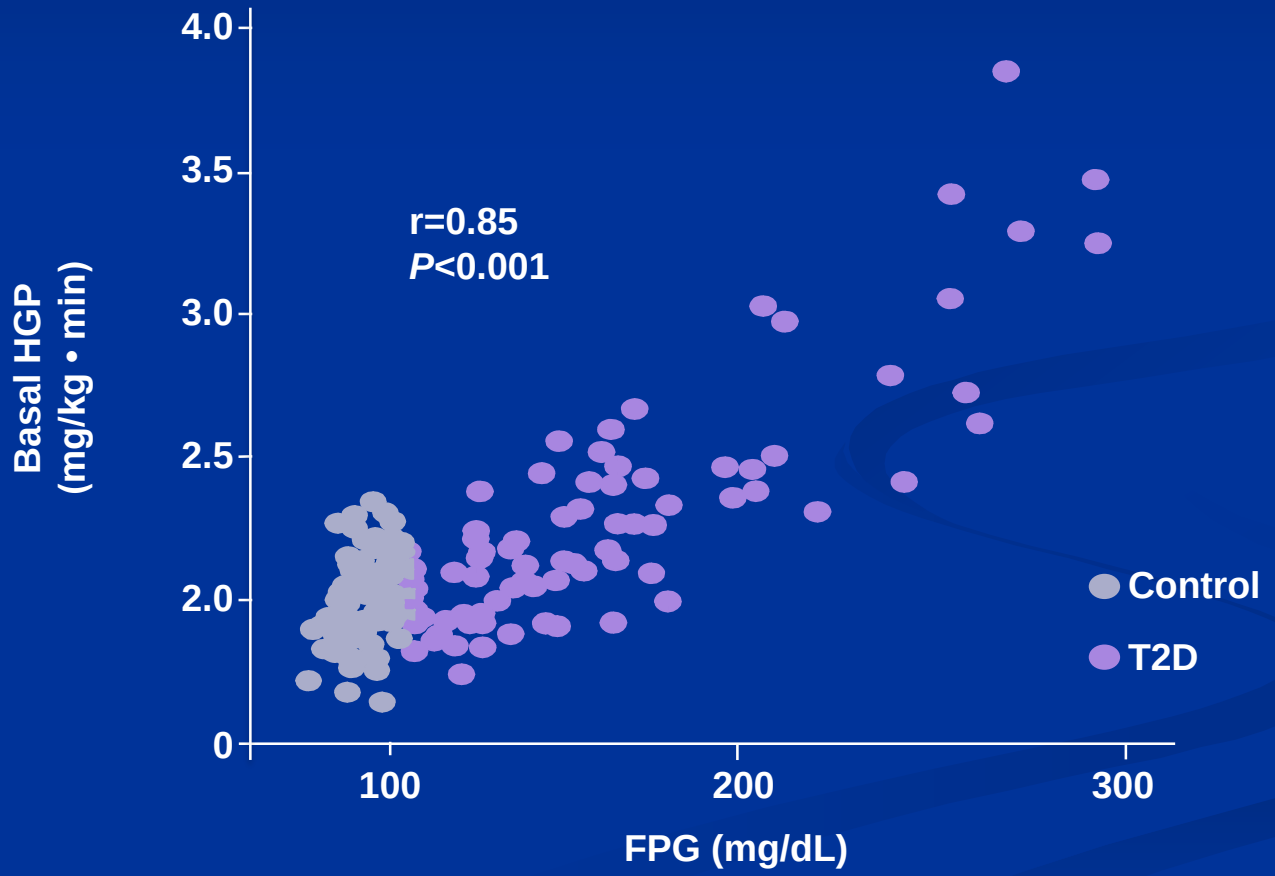




T2D, type 2 diabetes.

DeFronzo RA. *Diabetes*. 2009;58:773-795; DeFronzo RA, et al. *J Clin Invest*. 1985;76:149-155.

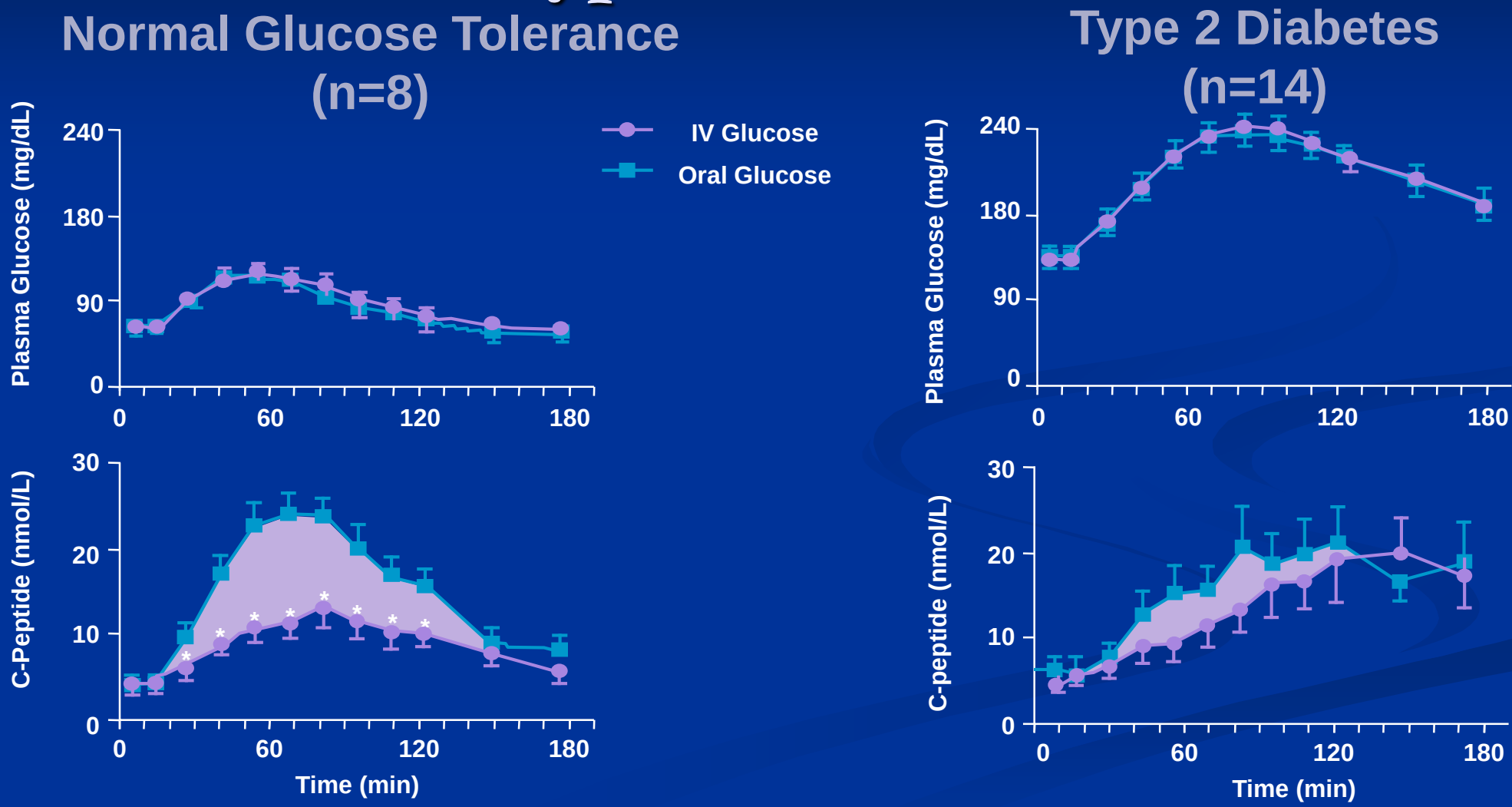
Elevated Fasting Glucose in Type 2 Diabetes Results From Increased HGP



FPG, fasting plasma glucose; HGP, hepatic glucose production; T2D, type 2 diabetes.

DeFronzo RA, et al. *Metabolism*. 1989;38:387-395.

The Incretin Effect Is Diminished in Type 2 Diabetes



*$P \leq .05$.

Nauck M, et al. *Diabetologia*. 1986;29:46-52.

Actions of GLP-1 and GIP

GLP-1

- Released from L cells in ileum and colon
- Stimulates insulin release from β-cell in a glucose-dependent manner
- Potent inhibition of gastric emptying
- Potent inhibition of glucagon secretion
- Reduction of food intake and body weight
- Significant effects on β-cell growth and survival

GIP

- Released from K cells in duodenum
- Stimulates insulin release from β-cell in a glucose dependent manner
- Minimal effects on gastric emptying
- No significant inhibition of glucagon secretion
- No significant effects on satiety or body weight
- Potential effects on β-cell growth and survival

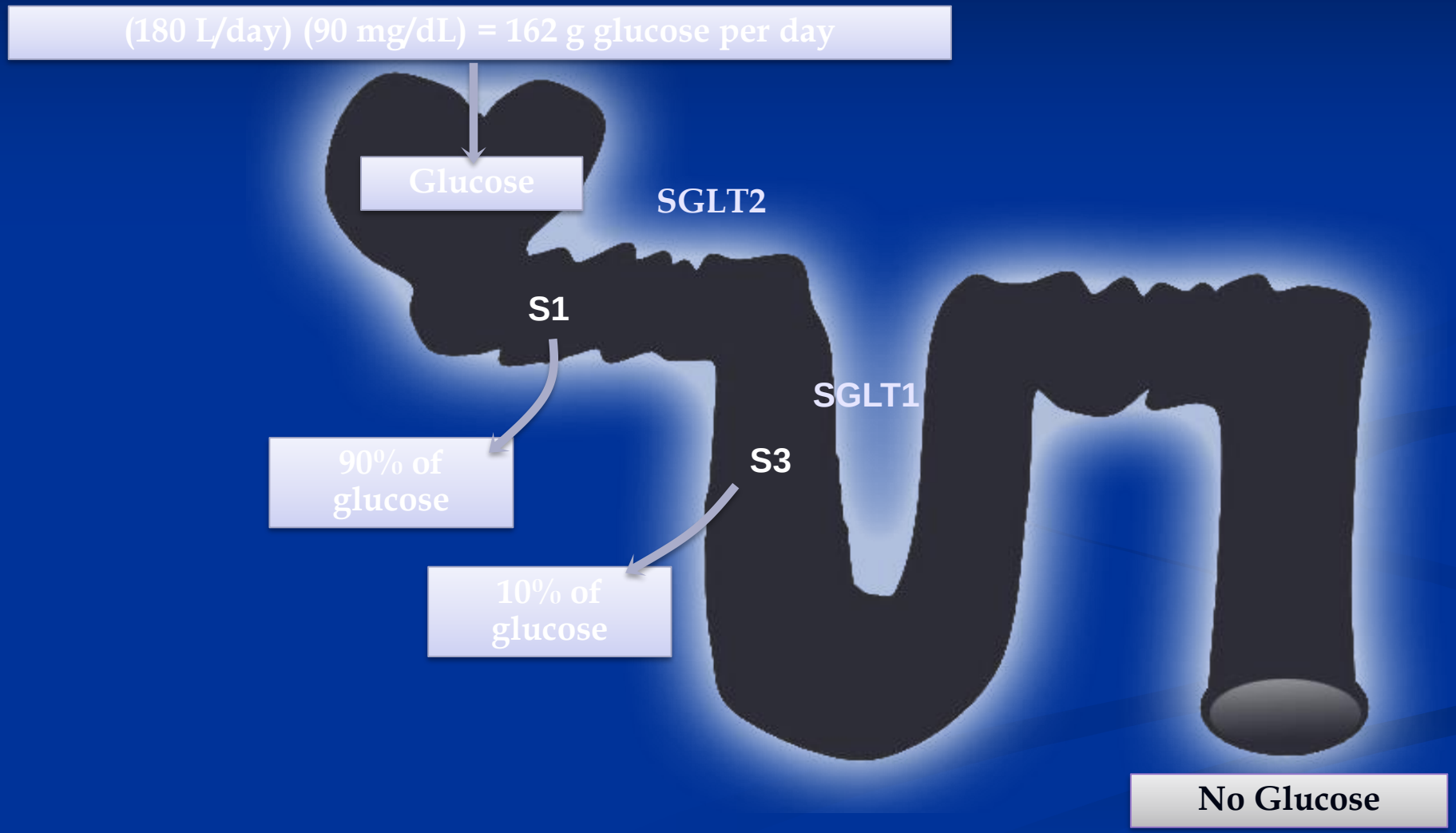
Drucker DJ. Diabetes Care 2003;26:2929-2940.

Renal Glucose Reabsorption in Type 2 Diabetes

- Sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2) reabsorb glucose in the proximal tubule of kidney
  - Ensures glucose availability during fasting periods
- Renal glucose reabsorption is increased in type 2 diabetes
  - Contributes to fasting and postprandial hyperglycemia
  - Hyperglycemia leads to increased SGLT2 levels, which raises the blood glucose threshold for urinary glucose excretion

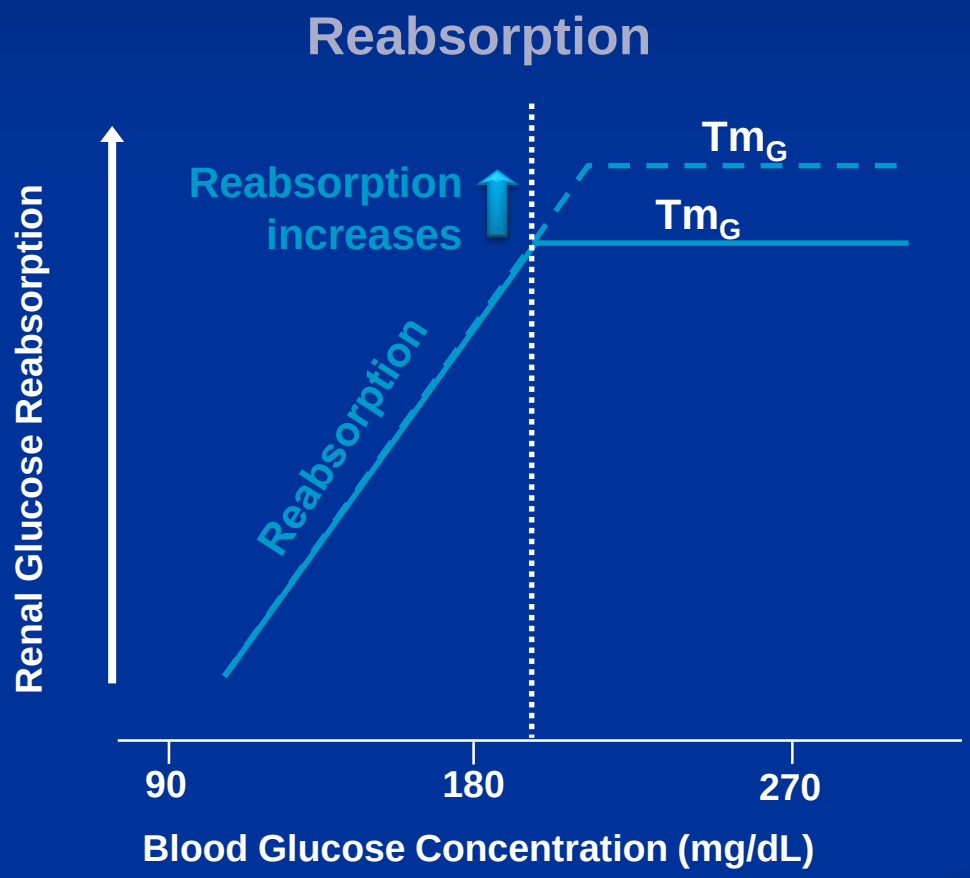
Wright EM, et al. *J Intern Med*. 2007;261:32-43.

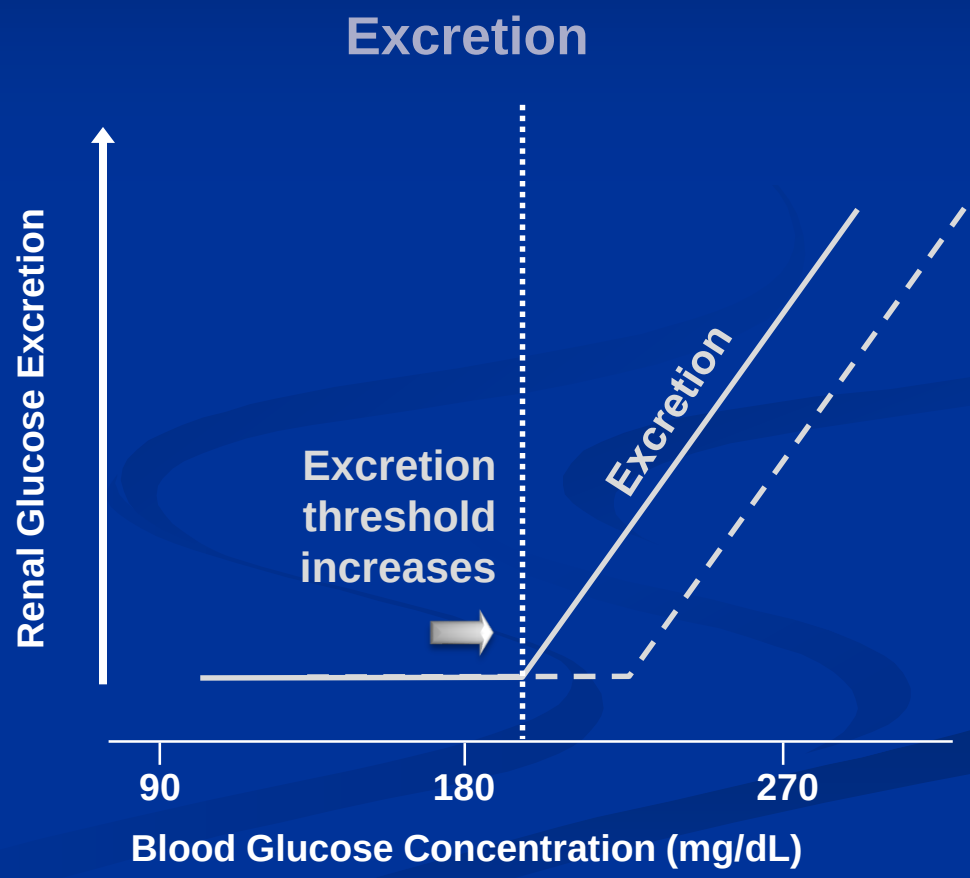
Normal Renal Handling of Glucose



Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790.

Increased SGLT2 Protein Levels Change Glucose Reabsorption and Excretion Thresholds

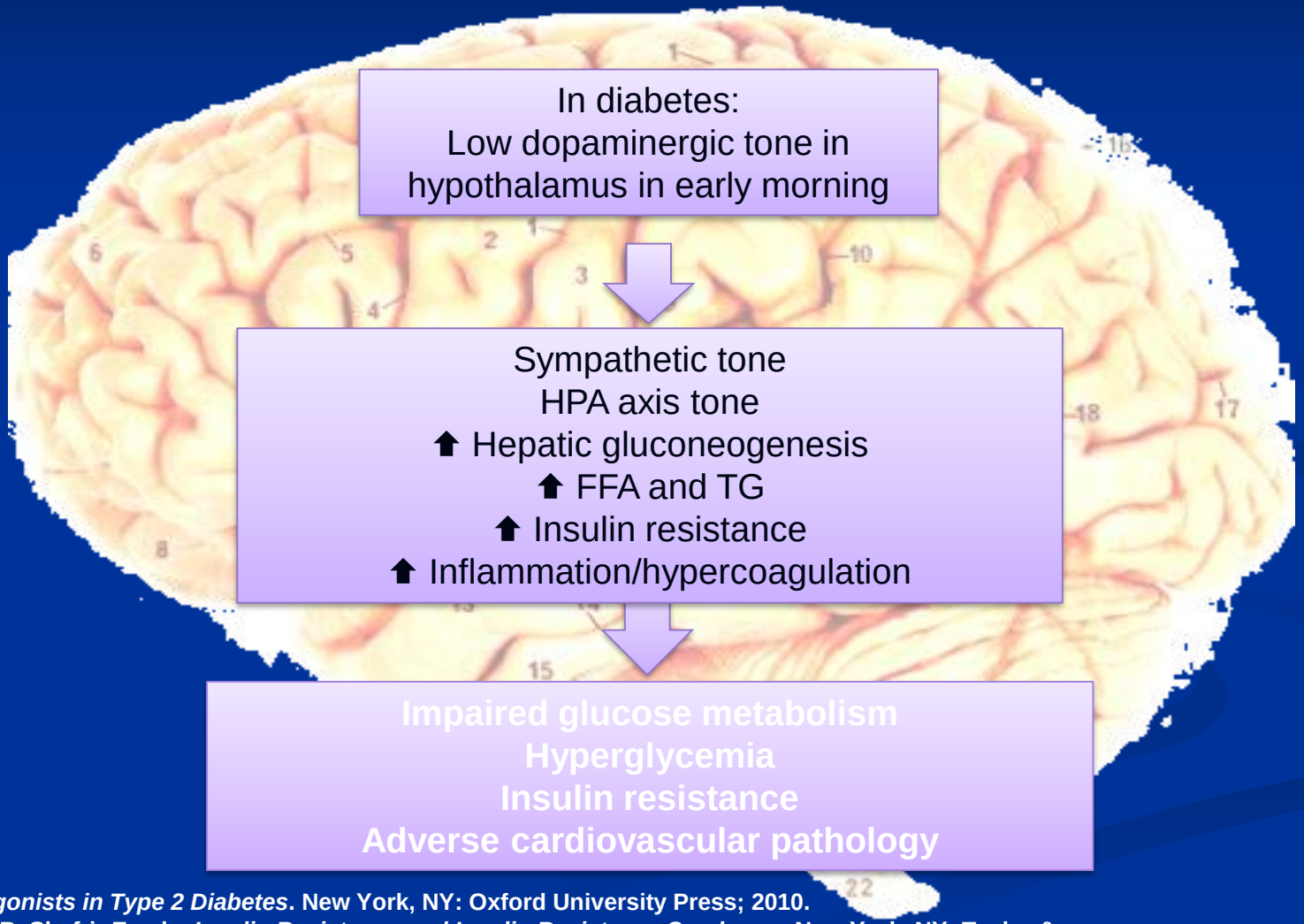




Tm_G, glucose transport maximum.

Abdul-Ghani MA, DeFronzo RA. Endocr Pract. 2008;14:782-790.

Hypothalamic Dopaminergic Tone and Autonomic Imbalance



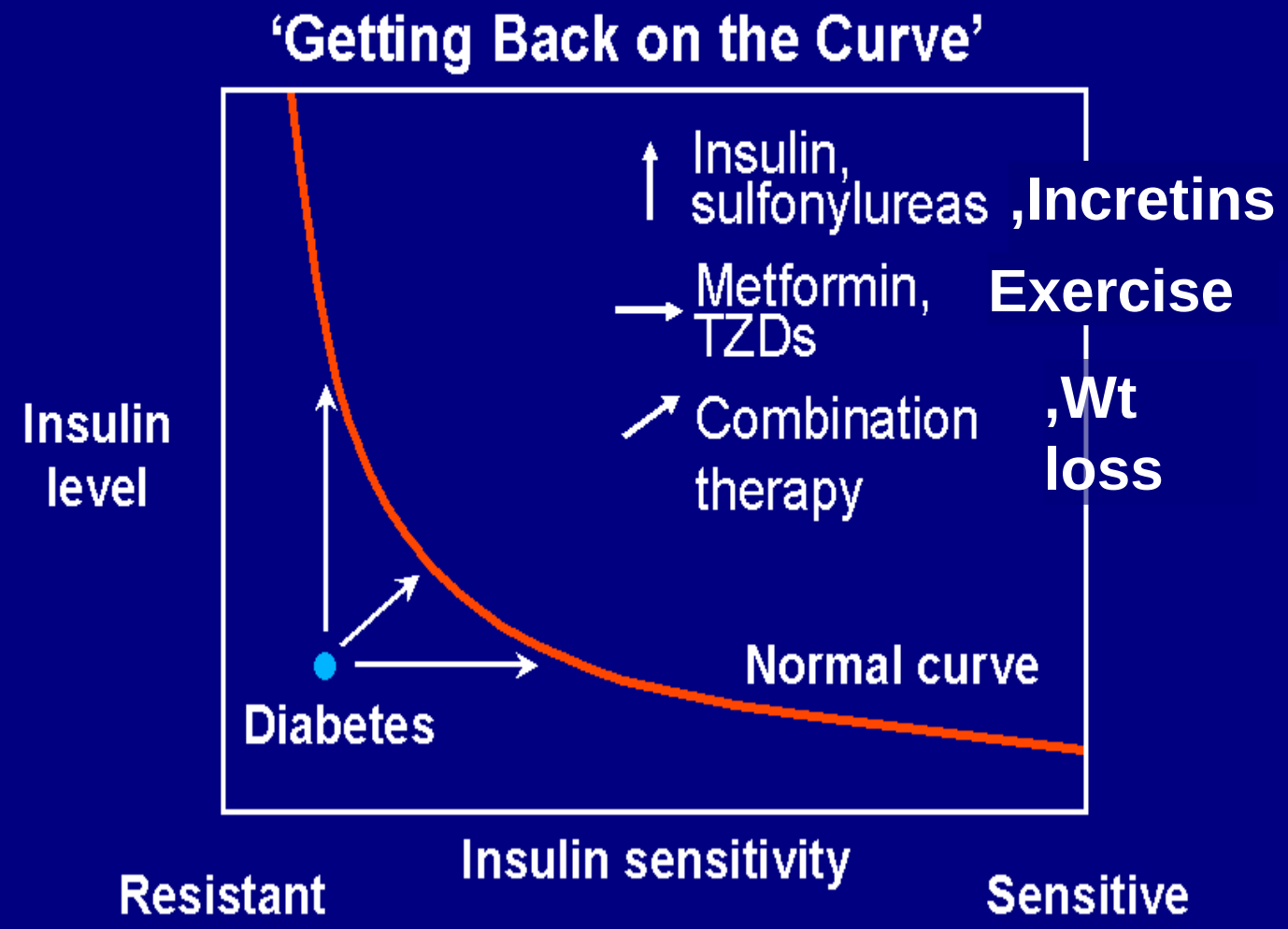
In diabetes:
Low dopaminergic tone in hypothalamus in early morning

Sympathetic tone
HPA axis tone
⬆ Hepatic gluconeogenesis
⬆ FFA and TG
⬆ Insulin resistance
⬆ Inflammation/hypercoagulation

Impaired glucose metabolism
Hyperglycemia
Insulin resistance
Adverse cardiovascular pathology

Fonseca V. *Dopamine Agonists in Type 2 Diabetes*. New York, NY: Oxford University Press; 2010.
Cincotta AH. In: Hansen B, Shafrir E, eds. *Insulin Resistance and Insulin Resistance Syndrome*. New York, NY: Taylor & Francis; 2002:271-312.

Treating Type 2 Diabetes: General Principles



Diagnosis of Type 2 Diabetes

Diagnostic Criteria for Prediabetes and Diabetes in Nonpregnant Adults

Normal	High Risk for Diabetes	Diabetes
FPG <100 mg/dL	IFG FPG ≥100-125 mg/dL	FPG ≥126 mg/dL
2-h PG <140 mg/dL	IGT 2-h PG ≥140-199 mg/dL	2-h PG ≥200 mg/dL Random PG ≥200 mg/dL + symptoms*
A1C <5.5%	5.5 to 6.4% For screening of prediabetes†	≥6.5% Secondary‡

*Polydipsia (frequent thirst), polyuria (frequent urination), polyphagia (extreme hunger), blurred vision, weakness, unexplained weight loss.

†A1C should be used only for screening prediabetes. The diagnosis of prediabetes, which may manifest as either IFG or IGT, should be confirmed with glucose testing.

‡Glucose criteria are preferred for the diagnosis of DM. In all cases, the diagnosis should be confirmed on a separate day by repeating the glucose or A1C testing. When A1C is used for diagnosis, follow-up glucose testing should be done when possible to help manage DM.

FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; PG, plasma glucose.

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

AACE Recommendations for A1C Testing

- A1C should be considered an additional optional diagnostic criterion, not the primary criterion for diagnosis of diabetes
- When feasible, AACE/ACE suggest using traditional glucose criteria for diagnosis of diabetes
- A1C is not recommended for diagnosing type 1 diabetes
- A1C is not recommended for diagnosing gestational diabetes

AACE. *Endocrine Pract*. 2010;16:155-156.

AACE Recommendations for A1C Testing

- A1C levels may be misleading in several ethnic populations (for example, African Americans)
- A1C may be misleading in some clinical settings
  - Hemoglobinopathies
  - Iron deficiency
  - Hemolytic anemias
  - Thalassemias
  - Spherocytosis
  - Severe hepatic or renal disease
- AACE/ACE endorse the use of only standardized, validated assays for A1C testing

AACE. *Endocrine Pract*. 2010;16:155-156.

Glycemic Management of Type 2 Diabetes

THERAPEUTIC LIFESTYLE CHANGE

LIFESTYLE THERAPY

RISK STRATIFICATION FOR DIABETES COMPLICATIONS

INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

Nutrition	• Maintain optimal weight • Calorie restriction (if BMI is increased) • Plant-based diet; high polyunsaturated and monounsaturated fatty acids	• Avoid *trans* fatty acids; limit saturated fatty acids	• Structured counseling • Meal replacement
Physical Activity	• 150 min/week moderate exertion (eg. walking, stair climbing) • Strength training • Increase as tolerated	• Structured program • Wearable technologies	• Medical evaluation/ clearance • Medical supervision
Sleep	• About 7 hours per night • Basic sleep hygiene	• Screen OSA • Home sleep study	• Referral to sleep lab
Behavioral Support	• Community engagement • Alcohol moderation	• Discuss mood with HCP	• Formal behavioral therapy
Smoking Cessation	• No tobacco products	• Nicotine replace-ment therapy	• Referral to structured program

 DOI 10.4158/EP161682.CS

Components of Therapeutic Lifestyle Change

- Healthful eating
- Sufficient physical activity
- Sufficient sleep
- Avoidance of tobacco products
- Limited alcohol consumption
- Stress reduction

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

AACE Recommendations: Therapeutic Lifestyle Changes

Parameter	Treatment Goal
Weight loss (for overweight and obese patients)	Reduce by 5% to 10%
Physical activity	150 min/week of moderate-intensity exercise (eg, brisk walking) plus flexibility and strength training
Diet	• Eat regular meals and snacks; avoid fasting to lose weight • Consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants) • Understand Nutrition Facts Label information • Incorporate beliefs and culture into discussions • Use mild cooking techniques instead of high-heat cooking • Keep physician-patient discussions informal

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

AACE Recommendations: Healthful Eating

Carbohydrate	Specify healthful carbohydrates (fresh fruits and vegetables, legumes, whole grains); target 7-10 servings per day Preferentially consume lower-glycemic index foods (glycemic index score <55 out of 100: multigrain bread, pumpernickel bread, whole oats, legumes, apple, lentils, chickpeas, mango, yams, brown rice)
Fat	Specify healthful fats (low mercury/contaminant-containing nuts, avocado, certain plant oils, fish) Limit saturated fats (butter, fatty red meats, tropical plant oils, fast foods) and trans fat; choose fat-free or low-fat dairy products
Protein	Consume protein in foods with low saturated fats (fish, egg whites, beans); there is no need to avoid animal protein Avoid or limit processed meats
Micronutrients	Routine supplementation is not necessary; a healthful eating meal plan can generally provide sufficient micronutrients Chromium; vanadium; magnesium; vitamins A, C, and E; and CoQ10 are not recommended for glycemic control Vitamin supplements should be recommended to patients at risk of insufficiency or deficiency

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.

AACE Recommendations: Medical Nutritional Therapy

- Consistency in day-to-day carbohydrate intake
- Adjusting insulin doses to match carbohydrate intake (eg, use of carbohydrate counting)
- Limitation of sucrose-containing or high-glycemic index foods
- Adequate protein intake
- "Heart-healthy" diets
- Weight management
- Exercise
- Increased glucose monitoring

Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87.