

Diabetes Pathophysiology and Treatment Strategies

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Diabetes: Pathophysiology and Treatment Strategies

Beth Careyva, M.D.
October 31, 2014
Lehigh University
Bioscience in the 21st Century



Objectives

- Review the epidemiology and trends of diabetes
- Discuss the pathophysiology of diabetes
- Delineate treatment strategies including lifestyle modification and medications



Epidemiology

- 11.3% of those over the age of 20 living with DM2 in the US¹
- World Health Organization estimates 7th leading cause of death by 2030²
- More than \$300 billion spent on diabetes-related medical costs in 2012³



1. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.

2. World Health Organization. Diabetes Fact Sheet No. 312. Reviewed October 2013. www.who.int/mediacentre/factsheets/fs312/en/. Accessed May 9, 2014.

3. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013;36:1033-1046.

CDC Fact Sheet

National Diabetes Fact Sheet, 2011



FAST FACTS ON DIABETES

*Diabetes affects 25.8 million people
8.3% of the U.S. population*

DIAGNOSED
18.8 million people

UNDIAGNOSED
7.0 million people

All ages, 2010

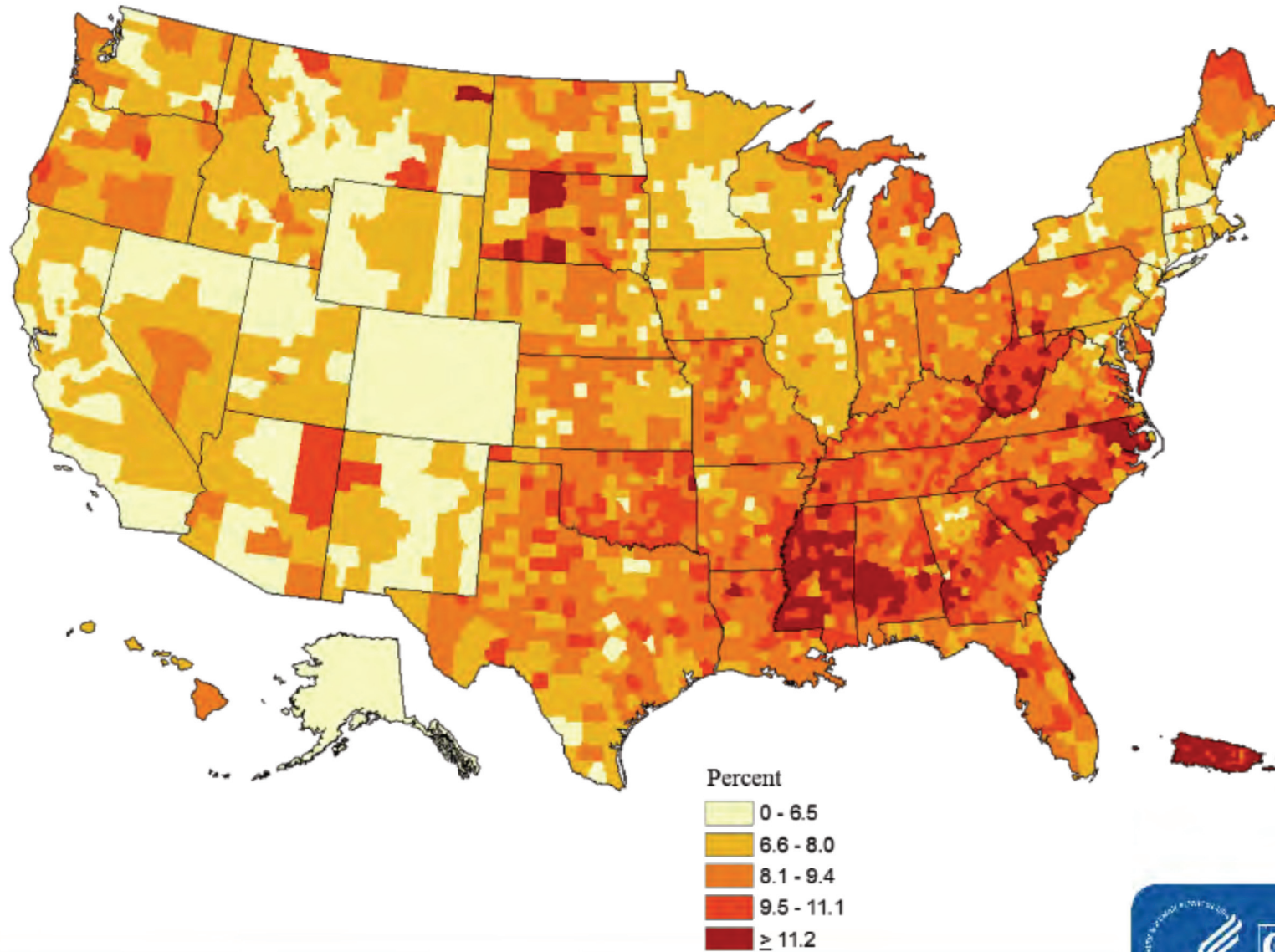
- Among U.S. residents aged 65 years and older, 10.9 million, or 26.9%, had diabetes in 2010.
- About 215,000 people younger than 20 years had diabetes (type 1 or type 2) in the United States in 2010.
- About 1.9 million people aged 20 years or older were newly diagnosed with diabetes in 2010 in the United States.



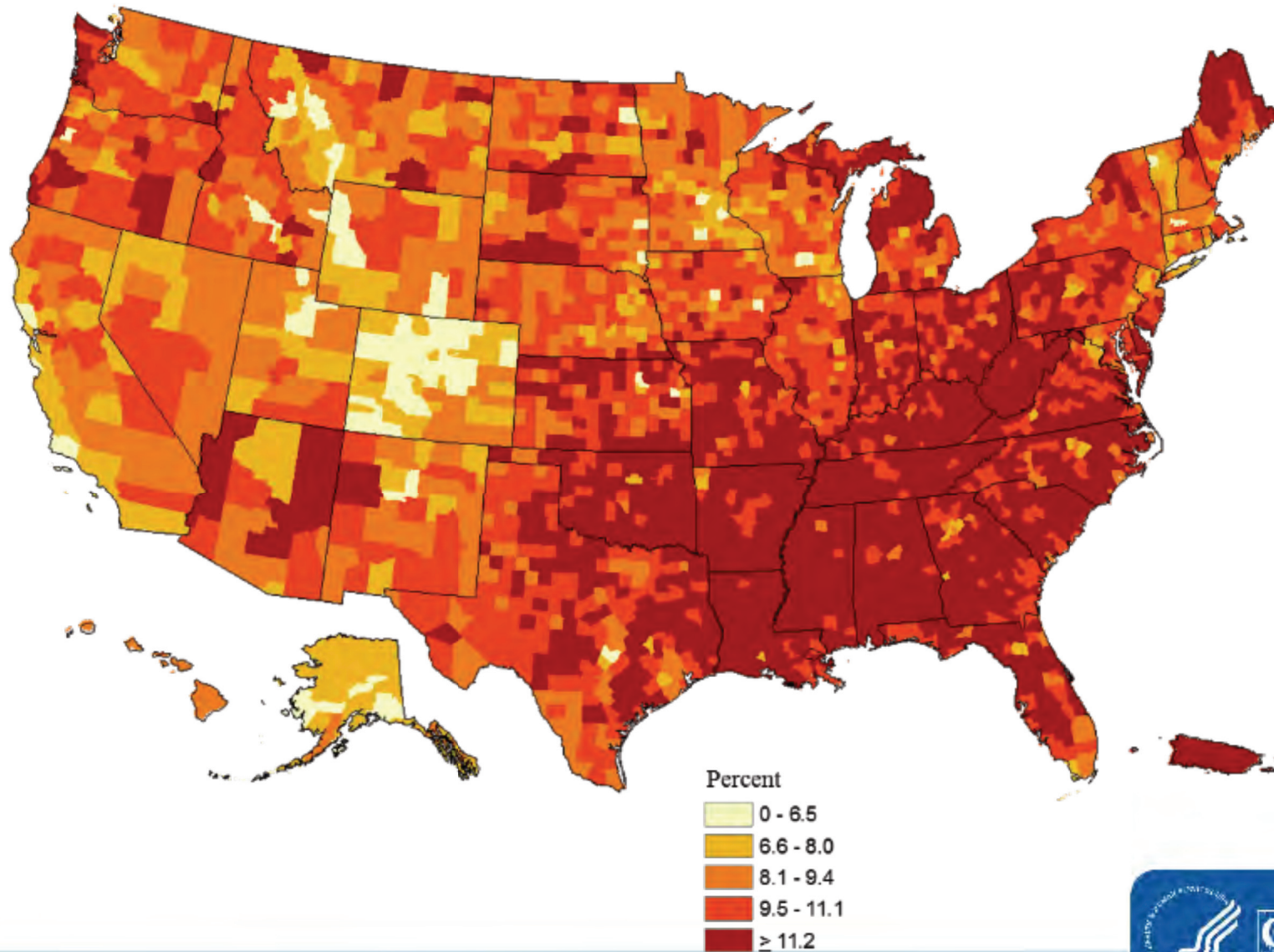
DM2 Epidemiology

- 90% of those with diabetes in the US, Canada, and Europe have type 2 diabetes

County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2004



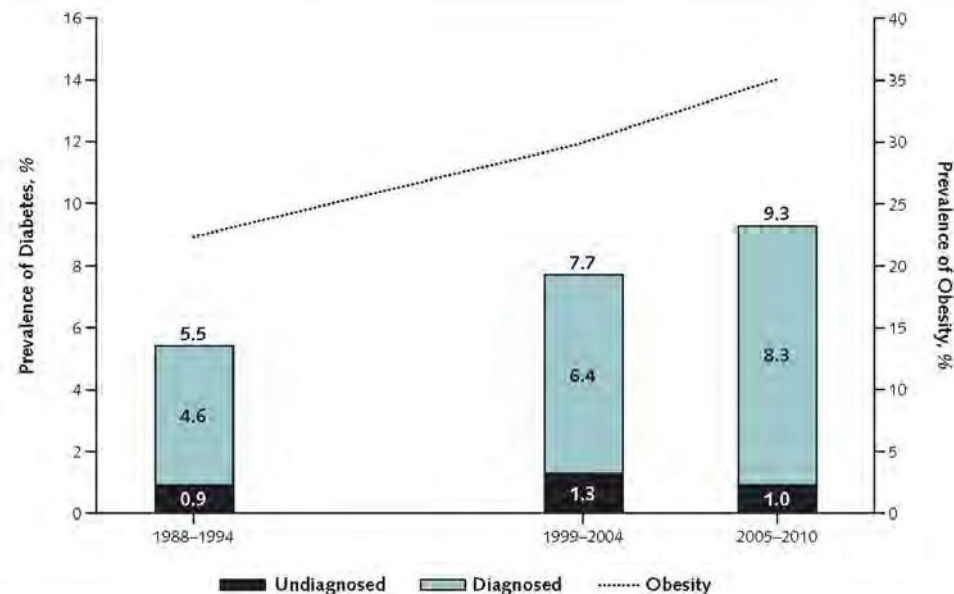
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years: United States 2011



Trends in Prevalence and Control of Diabetes in the United States, 1988–1994 and 1999–2010

Elizabeth Selvin, PhD, MPH; Christina M. Parrinello, MPH; David B. Sacks, MB, ChB; and Josef Coresh, MD, PhD

Figure 2. Prevalence of total confirmed diabetes and obesity.




Data from U.S. adults aged ≥ 20 y in NHANES 1988–1994, 1999–2004, and 2005–2010. Total confirmed diabetes was defined as diagnosed diabetes or undiagnosed diabetes with diagnostic levels of both hemoglobin A_{1c} ($\geq 6.5\%$) and fasting glucose (7.0 mmol/L [≥ 126 mg/dL]). Obesity was defined as body mass index ≥ 30 kg/m²; 601 persons were missing body mass index data. Prevalence estimates for total confirmed diabetes and obesity were obtained using only the subsample of participants who attended the morning fasting session (7385 participants for 1988–1994, 5680 participants for 1999–2004, and 6719 participants for 2005–2010). The midpoint for obesity prevalence between 1988–1994 and 1999–2004 was calculated as the average of the prevalence of the 2 periods. NHANES = National Health and Nutrition Examination Survey.

Published Online: 03 December 2013

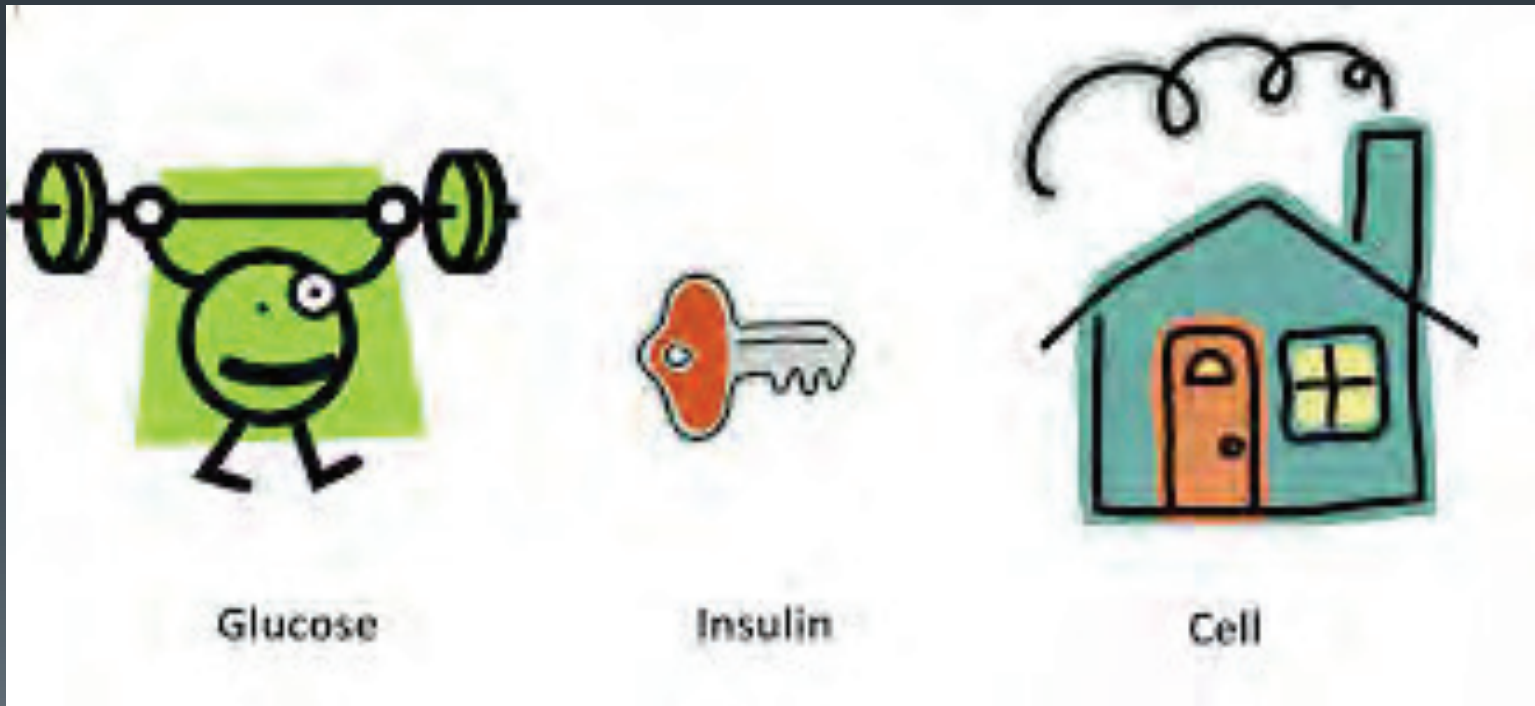
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Diabetes: a 21st century challenge

Prof [Paul Z Zimmet MD](#) , Prof [Dianna J Magliano PhD](#) ^a, Prof [William H Herman MD](#) ^b, Prof [Jonathan E Shaw MD](#) ^a

- Number of people with diabetes has more than doubled in the past 20 years
- Concerning is the number of new diagnoses in children and adolescents
- Need to work on **prevention** with focus on social and environmental factors

What is diabetes?





Definition of Diabetes

- Group of diseases resulting in **elevated blood glucose** levels
- Involves insufficient insulin or decreased response to insulin resulting in elevated blood glucose
- Glucose is the energy source for the cells



Types of Diabetes

- Type 1 Diabetes (DM1)
- Type 2 Diabetes (DM2)
- Prediabetes
- Gestational Diabetes

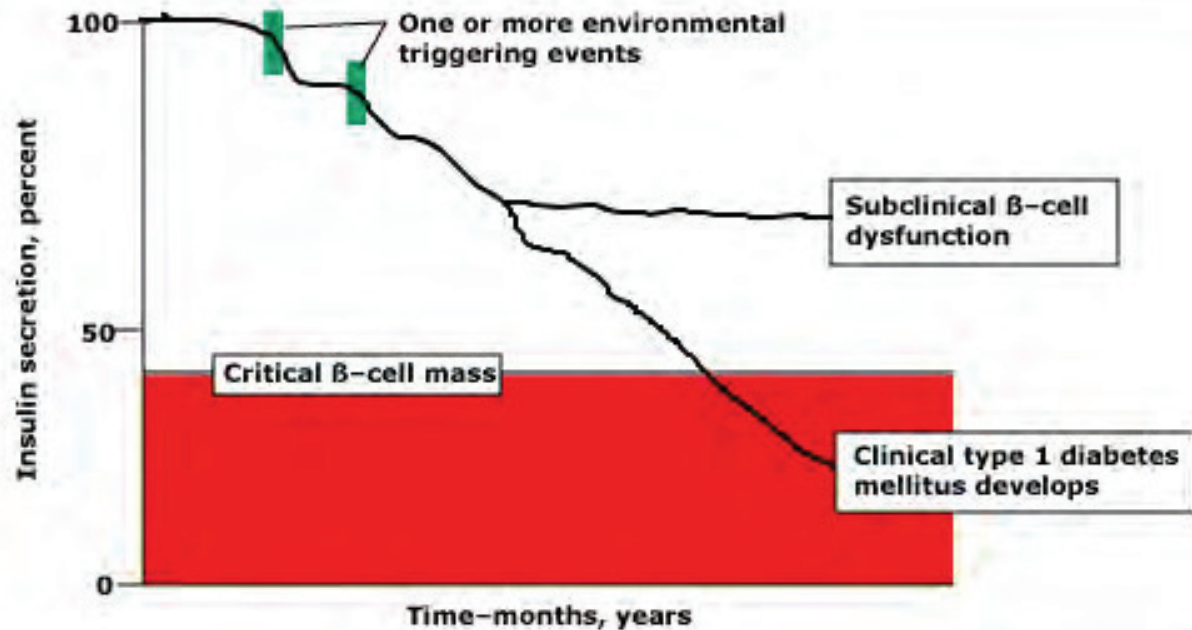
DM1

- **Autoimmune** destruction of insulin producing beta cells in pancreas
- Insulin dependent
- Typically childhood onset
- 5 – 10% of diabetes worldwide



dtd.ucsf.edu

Time course of type 1 diabetes mellitus



Time course of the development of type 1 diabetes. Genetic markers are present from birth, immune markers first appear at the time of the environmental triggering events, and sensitive metabolic markers of deficient insulin secretion begin to appear soon after the onset of beta-cell dysfunction. However, clinically evident type 1 diabetes does not occur until there has been a much greater loss of functioning beta-cell mass.

Diabetes Before Insulin

Diabetes, from the Greek word meaning "to pass through" or "pipe-like" has been claiming lives for thousands of years. A diabetic's body is unable to utilize food's nutrients as energy, causing extra sugar to collect in blood and urine (Bliss 20). Food simply "passes through" the body, without absorbing any nutrients.

Previous Treatments:

-Egyptians treated diabetes "with a combination of ground earth, water, bones, wheat, and lead" (Yuwiler 15)

-In the nineteenth century, physicians tried other common healing practices, such as bleeding, cupping or blistering patients.

-In the nineteenth and twentieth centuries, "opium seemed to reduce the despair of dying [diabetic] patients" (Yuwiler 16)



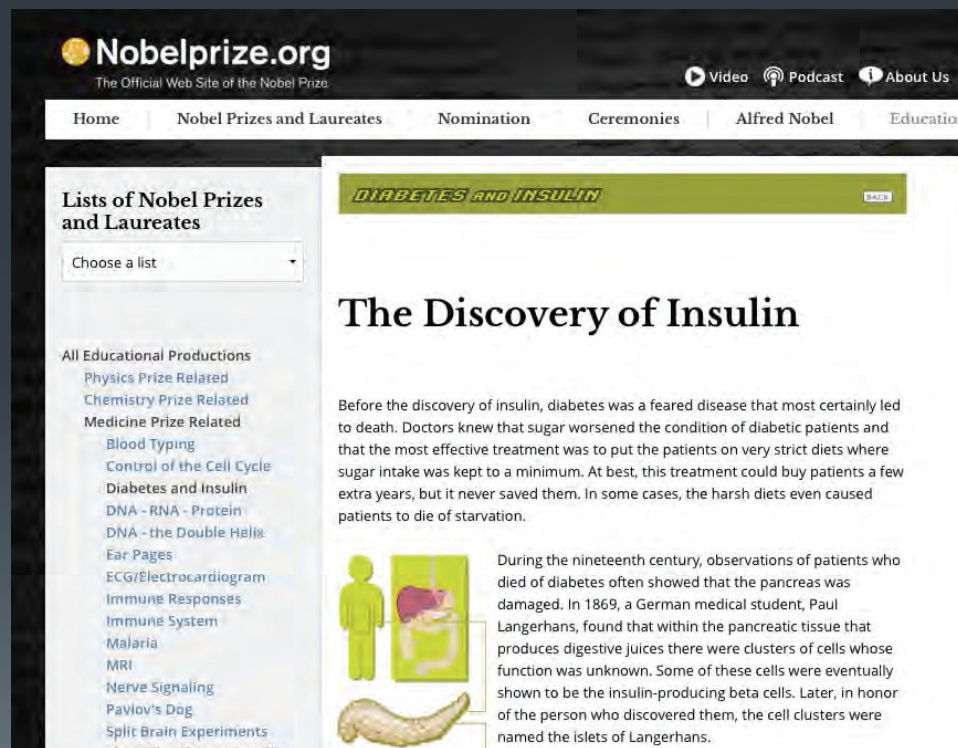
Eleventh century physician who searched for treatment.
(Yuwiler 16)

Slim Chances



With no effective treatment aside from a semi-starvation diet, a diabetic's outlook appeared grim. Before 1922, diabetic children rarely lived a year after diagnosis, five percent of adults died within two years, and less than 20 percent lived more than ten (Berger 57). Untreated diabetics faced blindness, loss of limbs, kidney failure, stroke, heart attack and death (Yuwiler 12).

Nobel Prize in 1923



The screenshot shows the Nobelprize.org website. The header includes the logo and navigation links: Home, Nobel Prizes and Laureates, Nomination, Ceremonies, Alfred Nobel, and Education. A sidebar on the left lists various educational productions, with 'Diabetes and Insulin' highlighted. The main content area features a green banner with the text 'DIABETES AND INSULIN' and a 'BACK' button. Below this is the title 'The Discovery of Insulin' and a paragraph of text. An illustration of a human figure with a highlighted pancreas and a separate image of the pancreas are also visible.

Nobelprize.org
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- Chemistry Prize Related
- Medicine Prize Related
 - Blood Typing
 - Control of the Cell Cycle
 - Diabetes and Insulin**
 - DNA - RNA - Protein
 - DNA - the Double Helix
- Ear Pages
- ECG/Electrocardiogram
- Immune Responses
- Immune System
- Malaria
- MRI
- Nerve Signaling
- Pavlov's Dog
- Split Brain Experiments
- The Cell and its Organelles

DIABETES AND INSULIN [BACK](#)

The Discovery of Insulin

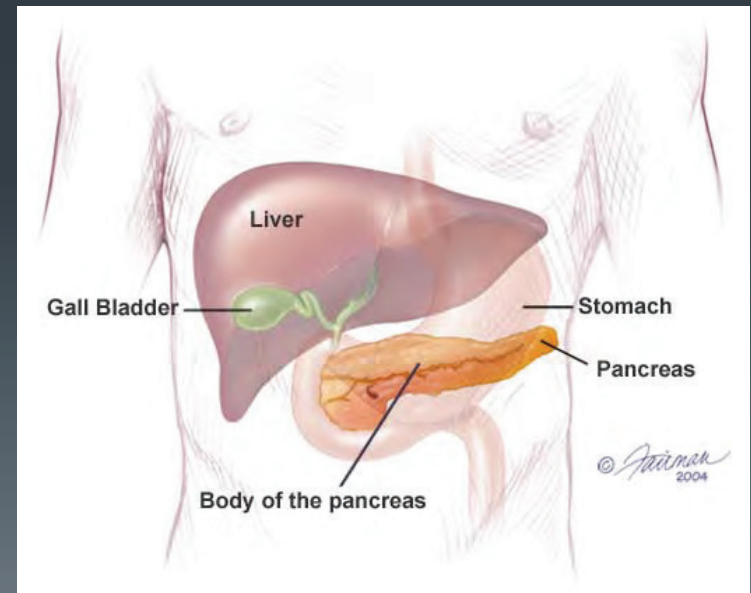
Before the discovery of insulin, diabetes was a feared disease that most certainly led to death. Doctors knew that sugar worsened the condition of diabetic patients and that the most effective treatment was to put the patients on very strict diets where sugar intake was kept to a minimum. At best, this treatment could buy patients a few extra years, but it never saved them. In some cases, the harsh diets even caused patients to die of starvation.

During the nineteenth century, observations of patients who died of diabetes often showed that the pancreas was damaged. In 1869, a German medical student, Paul Langerhans, found that within the pancreatic tissue that produces digestive juices there were clusters of cells whose function was unknown. Some of these cells were eventually shown to be the insulin-producing beta cells. Later, in honor of the person who discovered them, the cell clusters were named the islets of Langerhans.



Insulin

- Hormone that regulates the amount of glucose in the blood
- Produced by beta cells in pancreas
- Beta cells release insulin with each meal to help the body use or store glucose





Prediabetes

- Impaired fasting glucose or impaired glucose tolerance
- Increased risk for developing DM2
- Annual screening for diabetes recommended
- Intensive lifestyle modifications recommended



DM2

- Inadequate insulin production OR
- Insulin resistance OR
- **Inadequate insulin production AND insulin resistance**

- Linked to obesity
- Increased risk if African, Asian, Native American, Latino, or Pacific Islander



Gestational DM

- Increased risk if overweight or obese prior to pregnancy
- Affects 2 – 10% of women during pregnancy
- Increases risk of DM2



Summary

- Diabetes increasing in prevalence
- 4 Types: DM1, DM2, Prediabetes, and Gestational Diabetes
- Increased prevalence linked to obesity and environmental factors



Questions?



Pathophysiology



Pathophysiology

1. Impaired Insulin Secretion
2. Hyperglycemia
3. Insulin Resistance



Metabolic Defects

- Decreased glucose transport and utilization at the level of the muscle and adipose tissue
- Increased glucose production by the liver
- Decreased insulin secretion by the pancreas



What organs are involved?

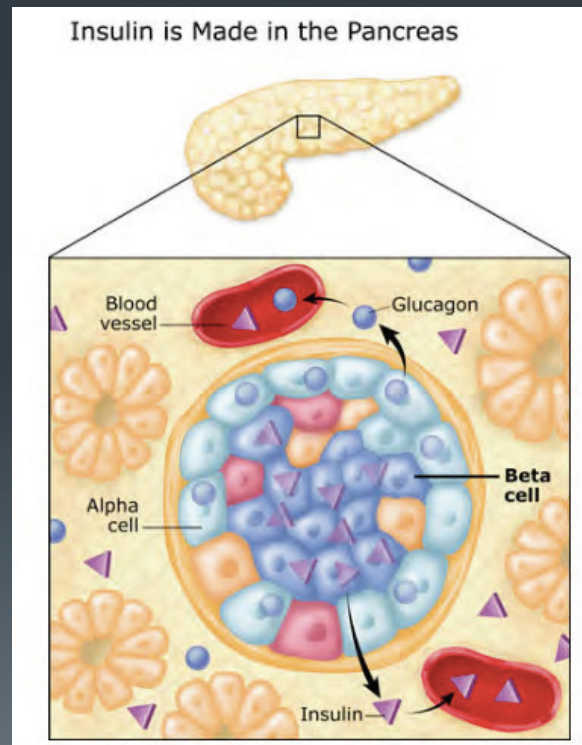
- Pancreas: beta cells secrete **insulin** and amylin, alpha cells secrete **glucagon**
- GI Tract: secrete **GLP-1** to signal beta cells to increase insulin and alpha cells to decrease glucagon
- Liver: stores glucose as glycogen, supplies glucose via gluconeogenesis and glyconeogenesis
- Muscles and adipose tissue: remove glucose from the blood
- Adrenal glands: secrete **epinephrine** and **cortisol**



Insulin Secretion

- From **beta** cells in pancreas
- Decreases over time in DM2
- May be exacerbated by hyperglycemia

Alpha and Beta Cells in Pancreas



dtc.ucsf.edu

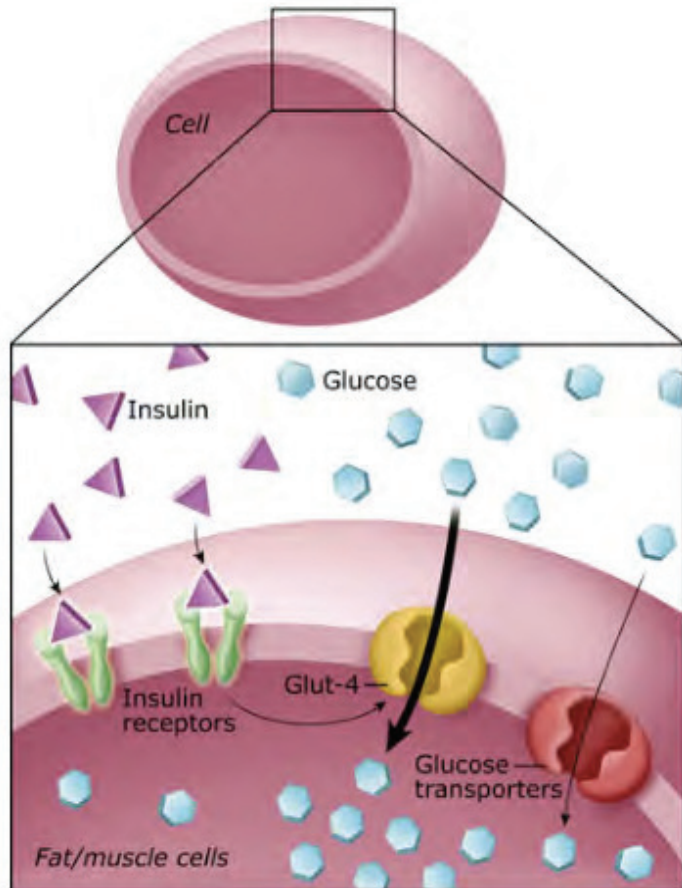


Insulin Resistance

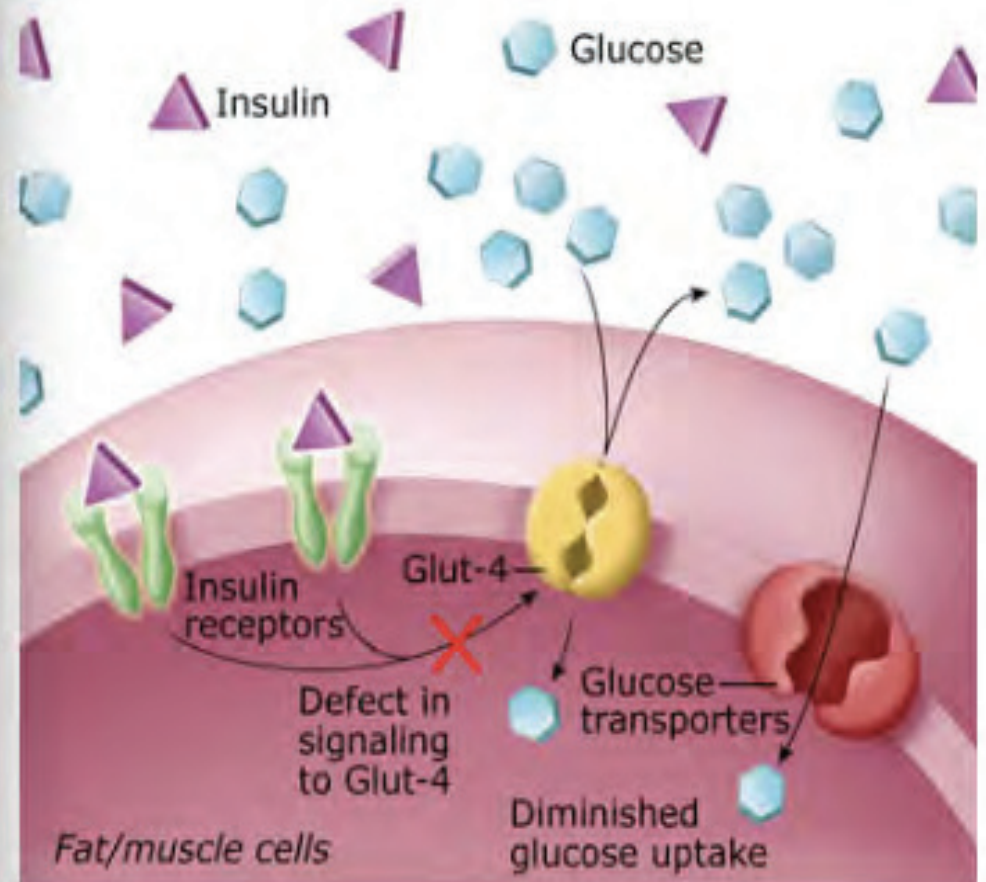
- Likely genetic component
- Exacerbated by inflammatory particles secreted by adipose tissue (leptin adiponectin, tumor necrosis factor alpha, and resistin)



The Effect of Insulin



Type 2 Diabetes: Insulin Resistance



Insulin and Glucagon

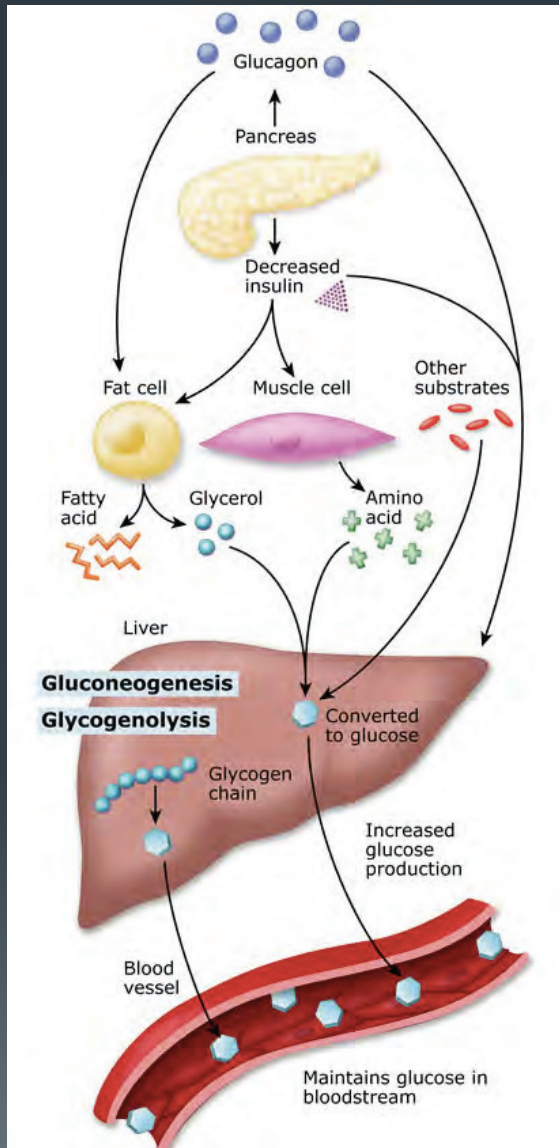




Glucagon

- Produced by **alpha** cells in pancreas
- Serves as counterbalance to insulin
- Signal liver to initiate glycogenesis

- In DM, glucagon levels rise inappropriately after eating

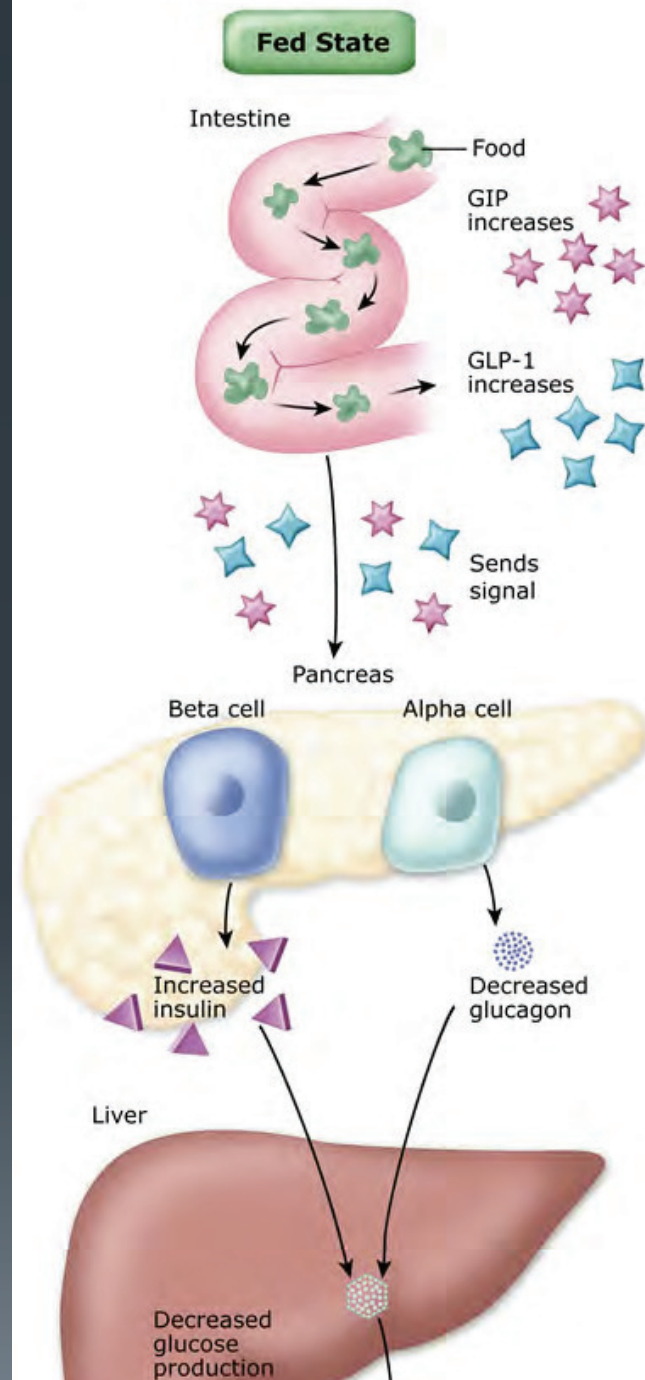


Fasting State

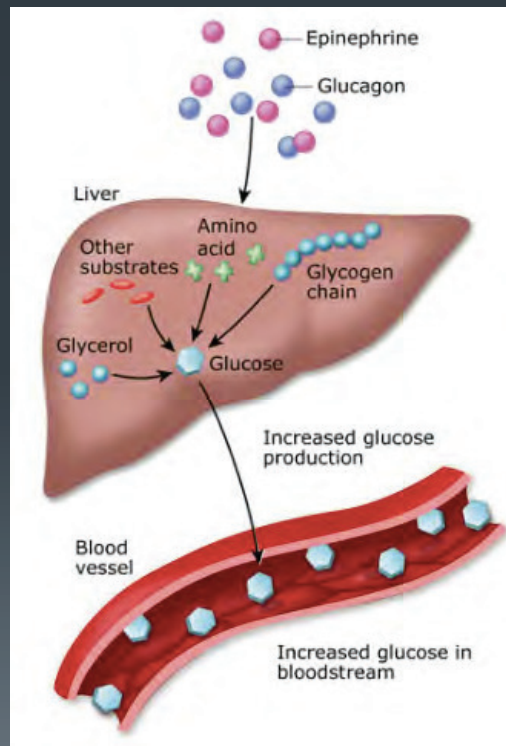
GLP-1

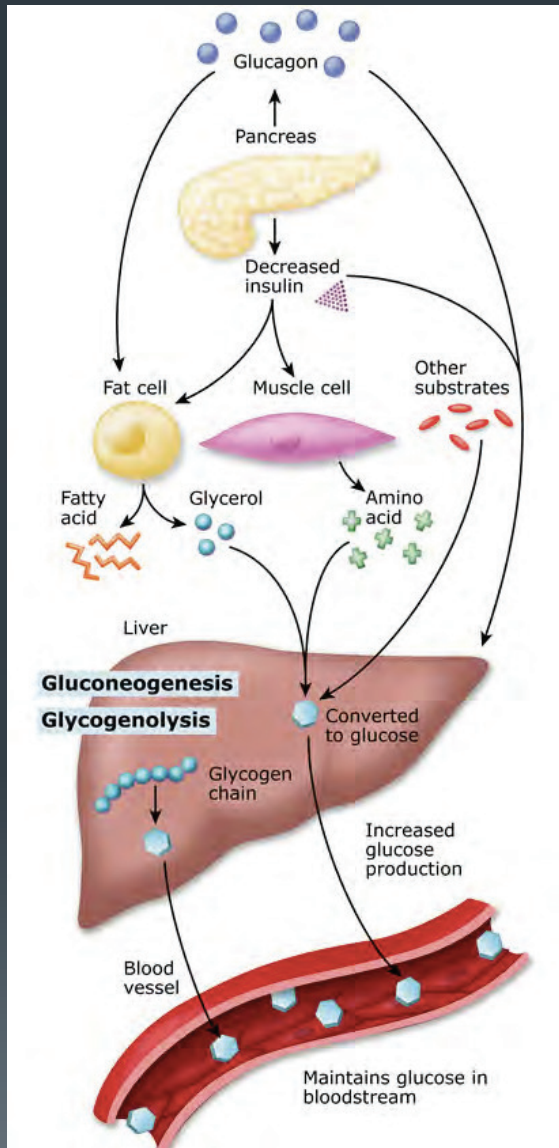
- Released from gut
- Signal beta cells to increase insulin and decrease glucagon

The Effect of GLP-1 and GIP



Epinephrine and Cortisol



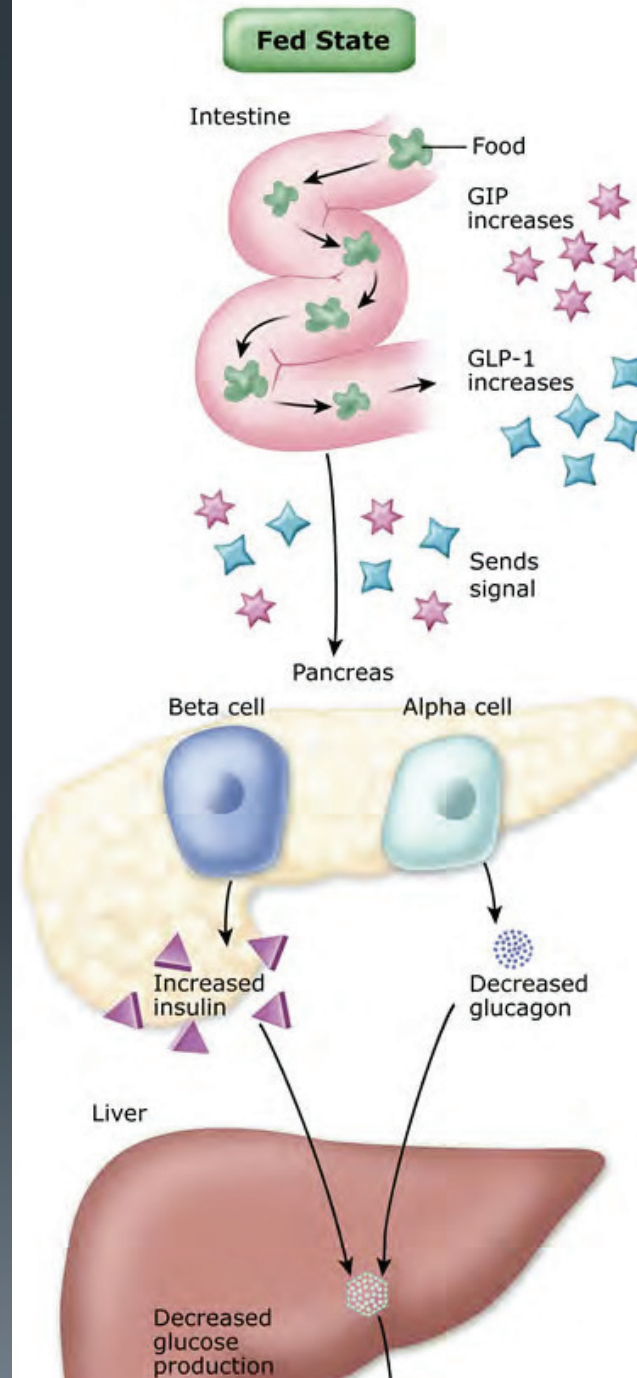


Fasting State

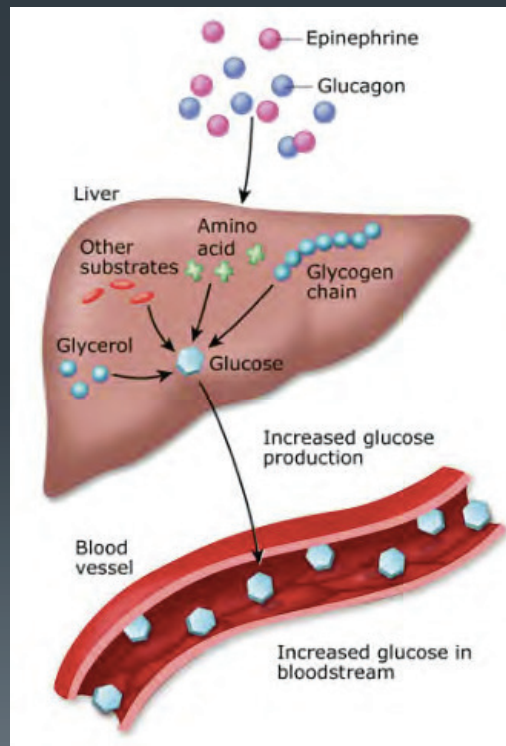
GLP-1

- Released from gut
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The Effect of GLP-1 and GIP



Epinephrine and Cortisol





What organs are involved?

- **Pancreas:** beta cells secrete insulin and amylin, alpha cells secrete glucagon
- **GI Tract:** secrete GLP-1 to signal beta cells to increase insulin and alpha cells to decrease glucagon
- **Liver:** stores glucose as glycogen, supplies glucose via gluconeogenesis and glyconeogenesis
- **Muscles and adipose tissue:** remove glucose from the blood
- **Adrenal glands:** secrete epinephrine and cortisol



Genetic Causes

- Lifetime risk of DM2 is 5-10 times higher in first-degree relatives
- Increased prevalence in certain ethnic groups, including people of Hispanic, African, and Asian decent

Environmental Causes

- Food sources
- Activity levels
- Built environment



Socioecological Determinants of Prediabetes and Type 2 Diabetes: Agenda for Action

Tiffany L. Gary-Webb, PhD, MHS, Aida L. Maisonet Giachello, PhD, Krista Maier, JD, and Heather Skrabak

- Need to recognize implications of built, food, school, and work environments
- Greater impact on groups with lower socioeconomic status



Summary

- Diabetes is the resultant hyperglycemia from inadequate insulin secretion, insulin resistance, or both
- It is progressive, with continual beta cell decline over time
- Genetic and environmental factors also play a role



Questions?



TREATMENT STRATEGIES



Goal

- Approach normoglycemia for most patients to decrease risk of microvascular and macrovascular complications



Treatment Strategies

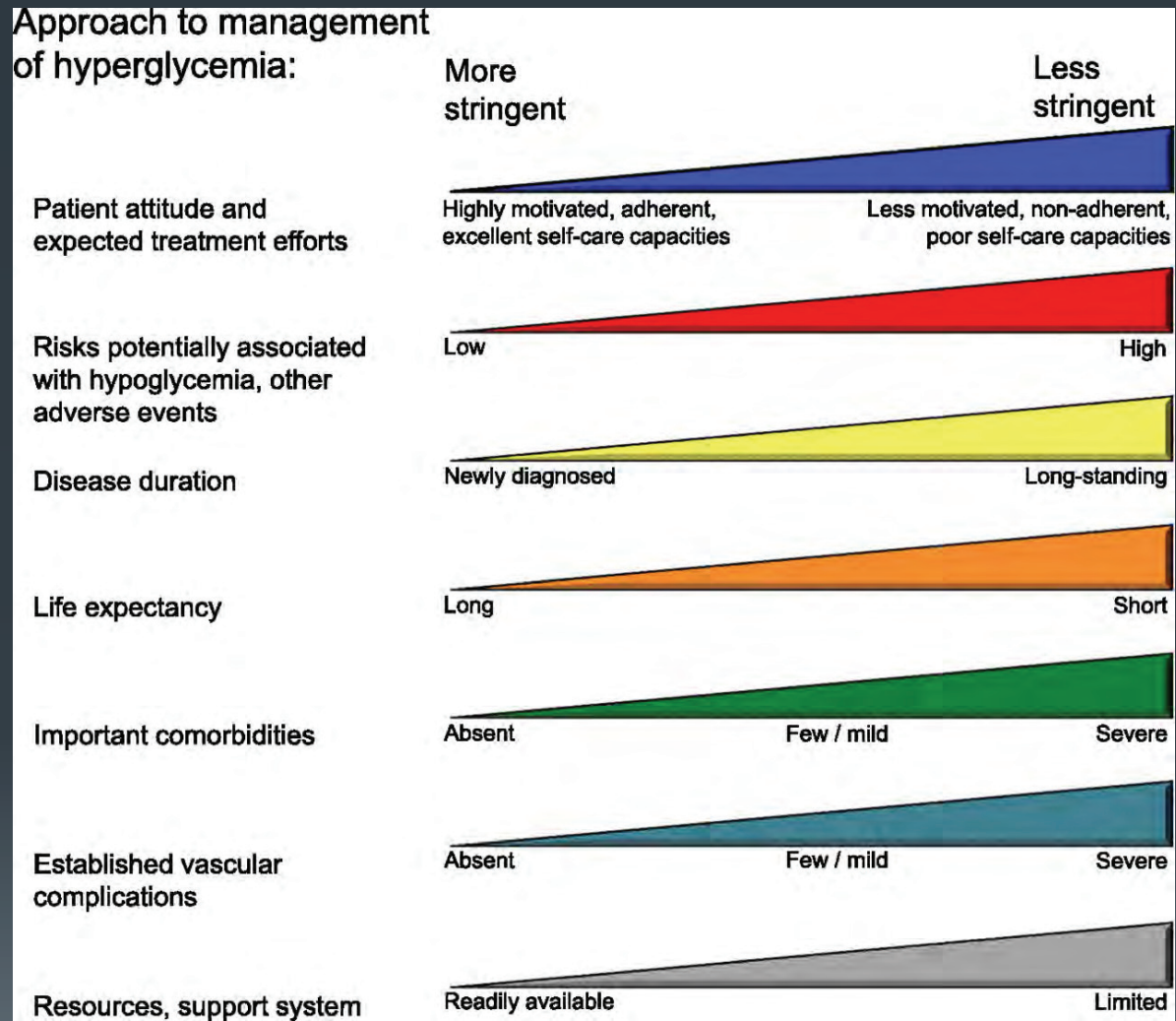
1. Lifestyle modifications: weight loss, dietary changes, increased physical activity
2. Self-monitoring
3. Medications: oral medications, injectable non-insulin medications, insulin
4. Screening for and preventing complications

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

- Tailored approach to treatment based on age, comorbidities, and availability of resources

Depiction of the elements of decision making used to determine appropriate efforts to achieve glycemic targets.



Inzucchi S E et al. Dia Care 2012;35:1364-1379





Lifestyle Modifications

- Low carbohydrate diets
- Increased physical activity
- Weight loss
- Bariatric surgery

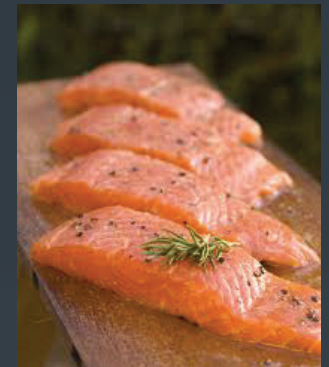


Bariatric surgery

- Patients followed for 15 years after surgery
- Associated with increased likelihood of long-term remission and decreased rates of microvascular and macrovascular complications

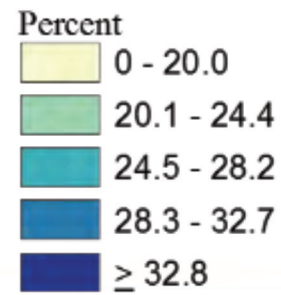
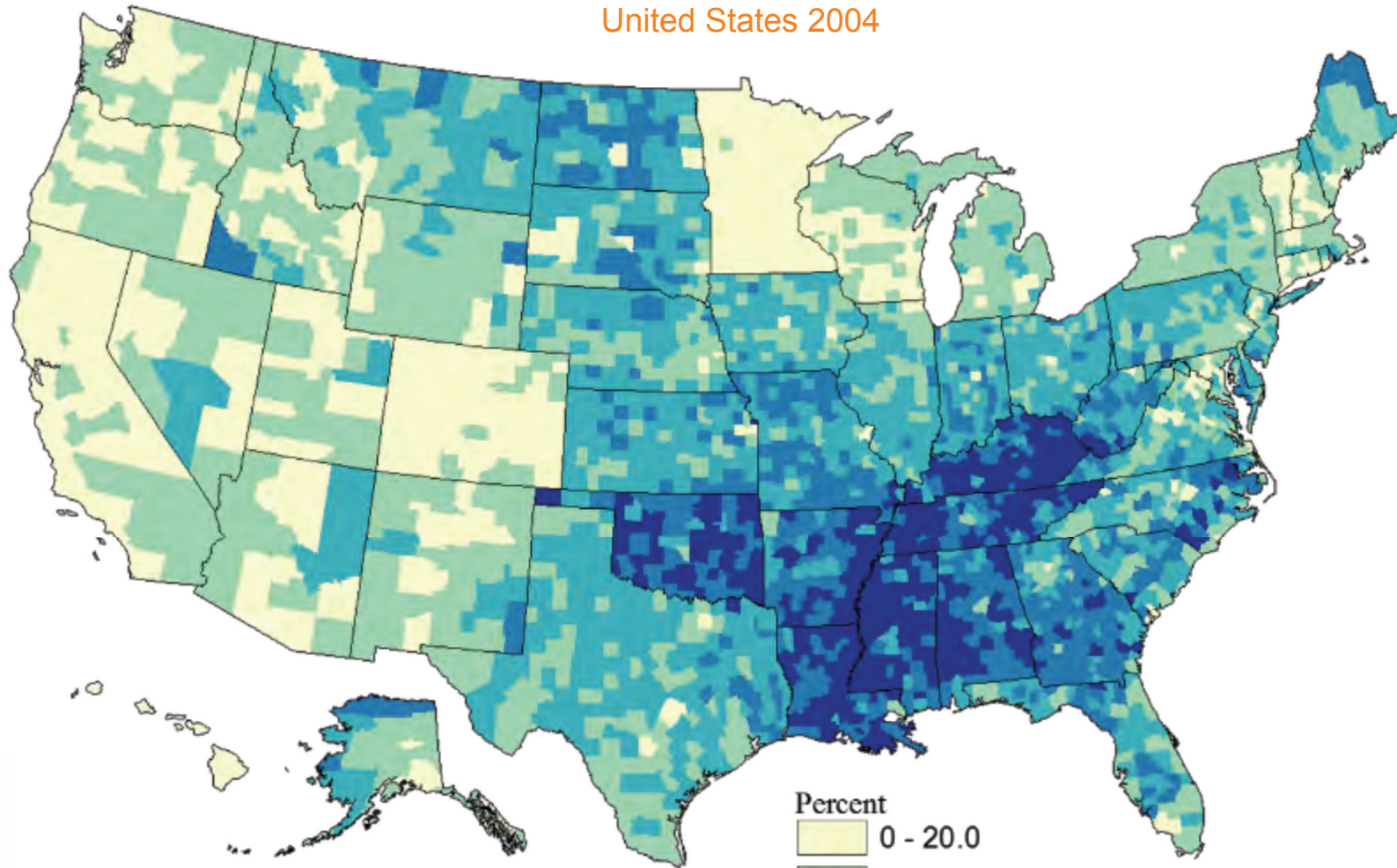
Diabetes Super Foods

- Beans
- Green leafy vegetables
- Sweet potatoes
- Berries
- Fish rich in omega 3 Fatty acids
- Fat-free milk and yogurt
- Whole grains
- Tomatoes
- Citrus fruits



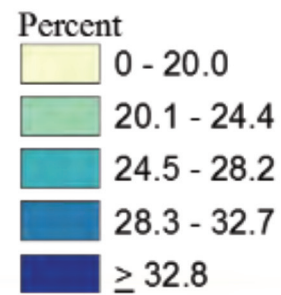
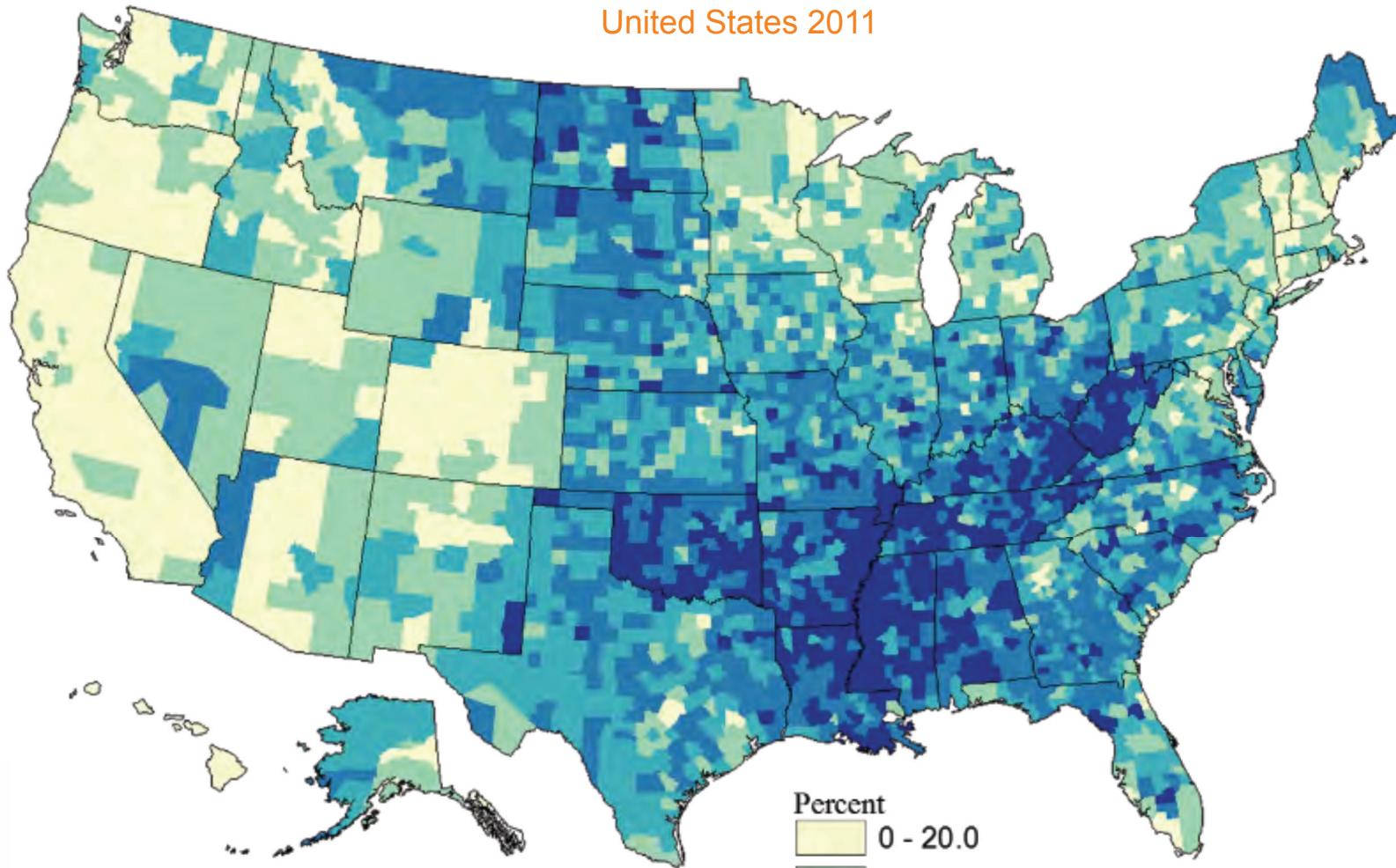
County-level Estimates of Leisure-time Physical Inactivity among Adults aged ≥ 20 years:

United States 2004

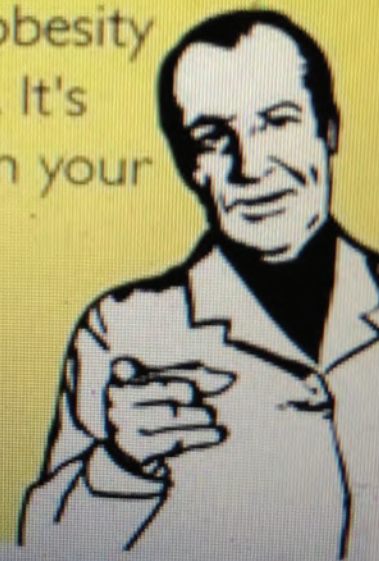


County-level Estimates of Leisure-time Physical Inactivity among Adults aged ≥ 20 years:

United States 2011



It's not that diabetes,
heart disease and obesity
runs in your family. It's
that no one runs in your
family.



som^{ee}cards
user card



DM Management

- Requires patient-activation and patient-clinician partnerships
- Gradual decline of beta cell function over time warrants changes to the care plan



Self-management

- Dietary changes
- Monitoring and recording blood glucose
- Keeping a log book of glucose readings
- Regular foot checks
- Laboratory tests



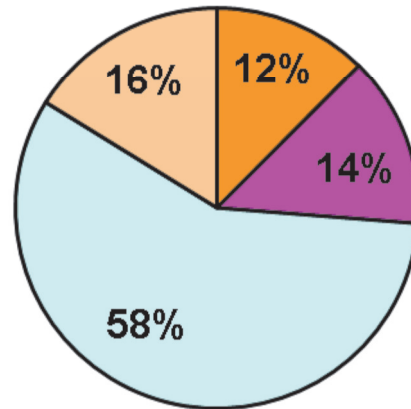
Hemoglobin A1c

- Glucose attaches to hemoglobin -> glycosylated hemoglobin
- Provides estimate of average glucose over the past 3 months
- May not be accurate if hemoglobin mutation



Medications

Percentage of adults with diagnosed diabetes receiving treatment with insulin or oral medication, United States, 2007–2009



■ Insulin only ■ Insulin and oral medication ■ Oral medication only ■ No medication

Source: 2007–2009 National Health Interview Survey.



Metformin

- First line oral agent
- Decreases hepatic glucose production
- Insulin sensitizer
- Shown to decrease mortality



Sulfonylureas

- Bind to component of ATP-dependent potassium channel in pancreatic beta cell (sulfonylurea 1 receptor)
- Stimulate insulin secretion from the pancreas
- Include glipizide, glyburide, gliclazide, and glimepiride

Incretin Based Therapies (DPP-4 Inhibitors, GLP-1 Agonist)

- DPP-4 inhibitors result in increased GLP-1
- GLP-1 is produced by small intestines in response to food
- GLP-1 Agonists bind to GLP-1 receptors and stimulate insulin release
- Both mechanisms achieve same goal of glucose-dependent insulin release from pancreas



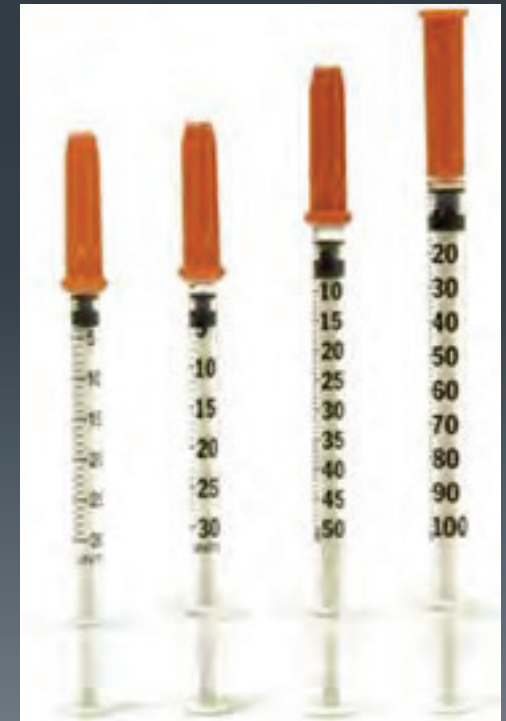


Thiazolidinediones

- Increase insulin sensitivity to remove glucose from the blood stream
- Act on muscles, adipose tissue, and the liver to increase glucose use and decrease glucose production
- Mechanism not fully understood
- Bind to peroxisome proliferator-activated receptors to regulate gene expression

Insulin

- Secreted with meals and in a pulsatile manner for basal level
- ~50% of insulin secretion is basal with the remaining being secreted around meals





Types of Insulin

- Rapid-acting
- Regular or Short-acting
- Intermediate-acting
- Long-acting



Modes of Insulin Administration

- Injection from insulin in bottle
- Injection from insulin pen
- Insulin pumps
 - More flexibility in dosing
 - Fewer highs and lows



Why is insulin not a pill?

- Insulin would be inactivated in the digestive system
- Needs to be injected to enter bloodstream



Summary

- Most effective treatment strategies combine lifestyle changes, self-care, medications, and prevention of complications
- Most patients will eventually require insulin given progressive nature of the disease



How has treatment changed in the 21st century?

- Creation of additional oral medications
- More sophisticated insulin pumps
- Increased use of bariatric surgery
- Technology support for self management (telehealth, patient portals)



Innovations in Technology

What is **glooko**

Glooko's mobile, cloud based diabetes management system serves patients, providers & payers by syncing blood glucose data from [30+ meters to Apple & Android devices](#), facilitating patient lifestyle data aggregation, and layering on smart analytics for diabetes population management.

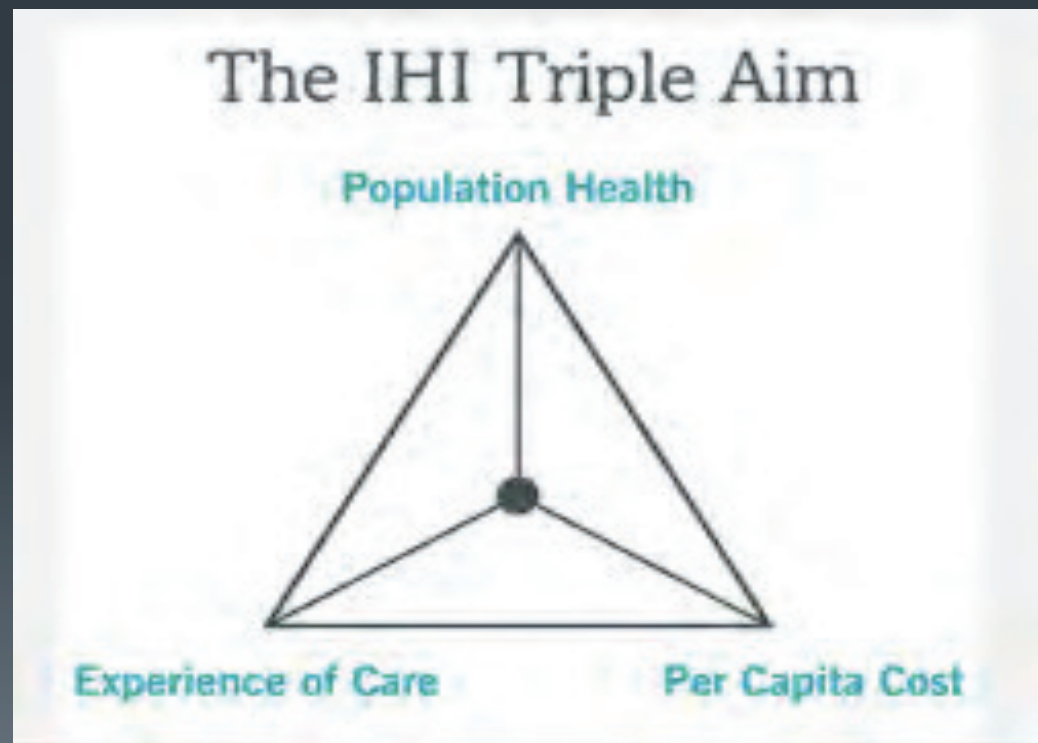
Glooko.com



More to come...

- Genetic testing to identify predisposition and which medications will be most effective
- New oral and injectable medications
- Health policy for prevention
- More pancreas transplants?

Institute for Healthcare Improvement Triple Aim



<http://www.ihl.org/Engage/Initiatives/TripleAim/Pages/default.aspx>



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1. Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2011.
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4. Zimmet PZ, Magliano DJ, Herman WH, et al. Diabetes: A 21st Century Challenge. *Lancet Diabetes Endocrinol.* 2013;2(1):56-64.
5. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: A patient-centered approach. *Diabetes Care.*2012;35(6):1364-1379.
6. Selvin E, Parrinello CM, Sacks DB, Coresh J. Trends in prevalence and control of diabetes in the United States, 1988-1994 and 1999-2010. *Ann Intern Med.* 2014;160:517-525.
7. Gary-Webb TL, Maisonet Giachello AL, Maier K, et al. Socioecological determinants of prediabetes and type 2 diabetes: agenda for action. *Clin Diabetes.*2014;32(3): 140-143.



With Gratitude

- Dr. Lowe-Krentz
- Dr. Ware





Questions?