

Diabetes Update

Exploring lifestyle and risk in preventing Type 2 Diabetes Mellitus



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MARCH 2017

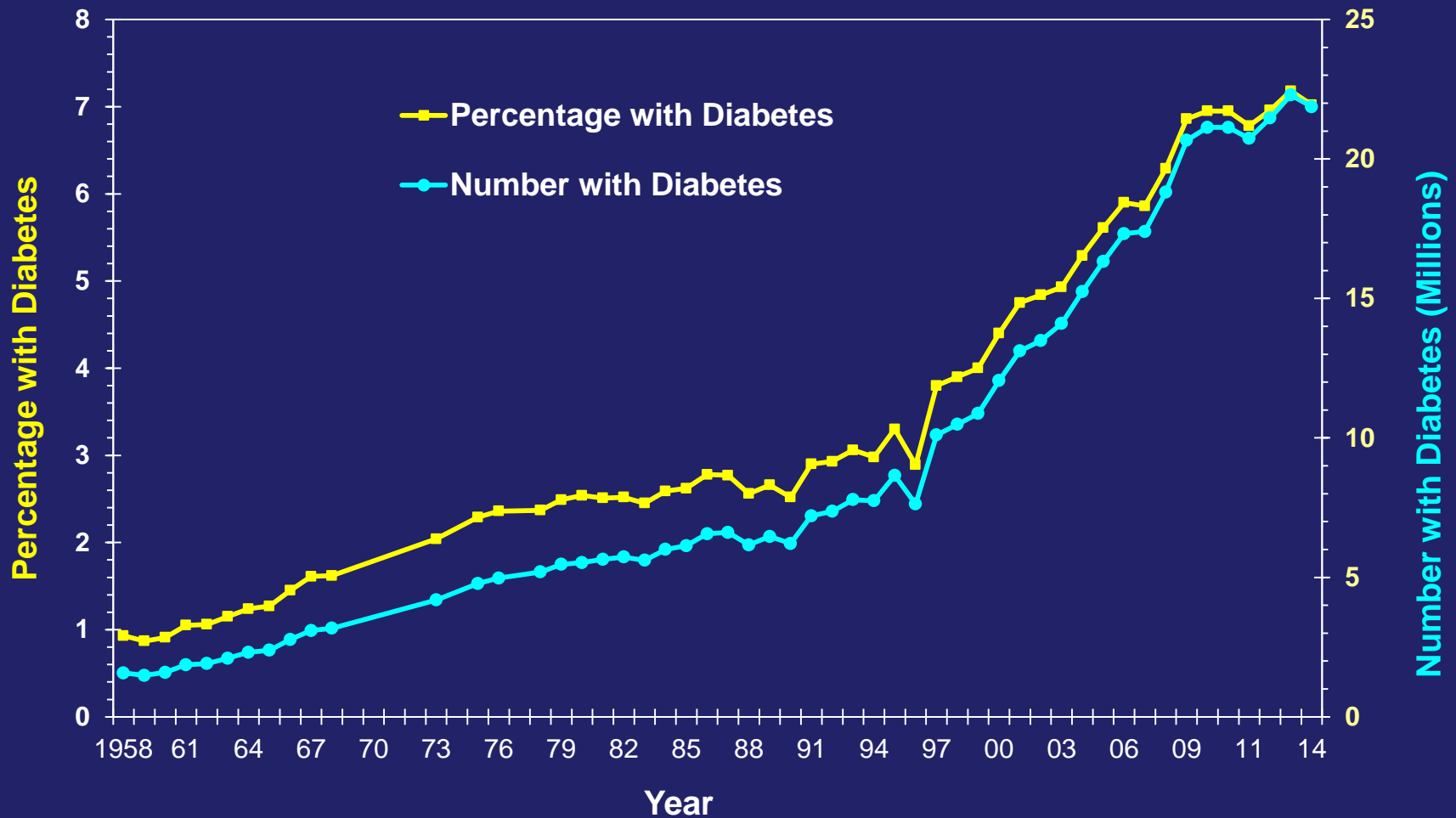
Objectives



1. Identify the prevalence of diabetes and obesity in the United States over time.
2. Review the classification and diagnosis of diabetes.
3. List recent diabetes and obesity guidelines.
4. List the pharmacologic agents used for treatment of diabetes.
5. Explain the recent changes to metformin labeling.
6. Describe adverse events associated with some oral antihyperglycemic agents.
7. Review the different types of insulin and describe new insulin therapies.
8. Identify the risk factors for DM Type 2.
9. Review the categories of increased risk for DM Type 2.
10. Discuss how to prevent/delay Type 2 DM.

*Focus is Type 2 DM-adult nonpregnant patient

Number and Percentage of U.S. Population with Diagnosed Diabetes, 1958-2014

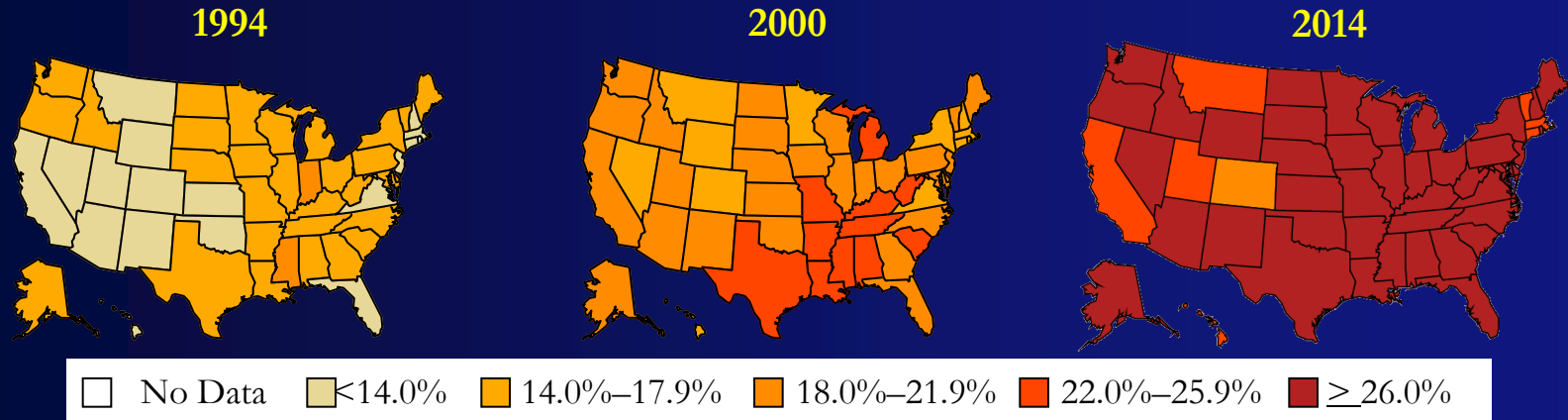


CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at <http://www.cdc.gov/diabetes/data>

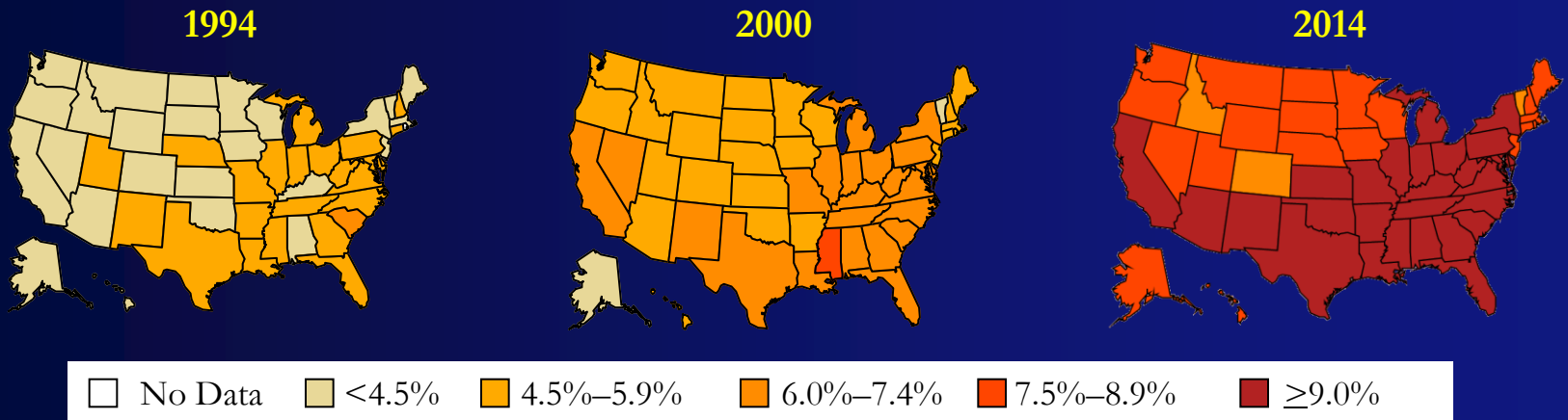


Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI ≥ 30 kg/m²)



Diabetes



NOTE: Survey method changes in 2011 may impact trends <http://www.cdc.gov/surveillancepractice/reports/brfss/brfss.html>
 CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at
<http://www.cdc.gov/diabetes/data>



Types of Diabetes



- **Appropriate nomenclature**
 - DM Type 1
 - Type 1 Diabetes
 - DM Type 2
 - Type 2 Diabetes

- **Old nomenclature; no longer used**
 - IDDM
 - NIDDM
 - Insulin dependent
 - Non-insulin dependent
 - Diabetic in reference to a person
 - ✦ Will no longer be used to refer to patients with diabetes
 - ✦ ADA position that diabetes does not define people

Classification of Diabetes



1. Type 1 Diabetes
2. Type 2 Diabetes
3. Gestational diabetes mellitus
4. Specific types of diabetes due to other causes

Classification of Diabetes



- **Type 1 Diabetes**
 - Previously referred to as juvenile onset or insulin dependent diabetes mellitus (IDDM)
 - Most commonly due to cellular mediated autoimmune pancreatic islet β cell destruction
 - ✦ Autoimmune markers:
 - Glutamic acid decarboxylase (GAD 65) antibodies
 - Islet cell antibodies (ICA)
 - Insulin autoantibodies (IAA)
 - Tyrosine phosphatases IA-2, and Ia-2 β
 - ZnT8
 - Ultimately leads to *absolute* insulin deficiency
 - ✦ Rate is variable
 - HLA associations
 - ✦ Linkage to DQA and DQB genes

Classification of Diabetes



- Type 2 diabetes
 - Previously referred to as adult onset or noninsulin dependent diabetes mellitus (NIDDM)
 - Results from *relative* insulin deficiency
 - ✦ Insulin secretion is defective or insufficient to compensate for insulin resistance
 - 90-95% (ADA guidelines)
 - Do not initially or may not ever require insulin therapy

Classification of Diabetes



- **Gestational Diabetes Mellitus (GDM)**
 - Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly preexisting diabetes

Classification of Diabetes



- Other specific types of diabetes:
 - Autosomal dominant genetic defects of pancreatic β cells
 - ✦ Maturity onset diabetes of the young (MODY)
 - Onset of hyperglycemia in late childhood or <25 years of age
 - Characterized by impaired insulin secretion with minimal or no defects in insulin action (in nonobese patients)
 - Autosomal dominant inheritance
 - 3 most common forms:
 - GCK-MODY (MODY 2)
 - Mild stable fasting hyperglycemia
 - Often do not require therapy except during pregnancy
 - HNF1A-MODY (MODY 3)
 - HNF4A-MODY (MODY 1)
 - ✦ Diseases of the exocrine pancreas
 - Cystic fibrosis
 - ✦ Drug or chemical induced diabetes
 - Glucocorticoid use
 - HIV/AIDs treatment
 - After organ transplantation

Usually respond well to low dose sulfonylureas

How is diabetes diagnosed?



- Fasting blood sugar ≥ 126 mg/dl
 - How is fasting defined?
 - ✦ Fasting is defined as no caloric intake for 8 hours.

OR

- 2 hour plasma glucose ≥ 200 mg/dl during an oral glucose tolerance test
 - How is the test performed? How much glucose is ingested?

OR

- HbA1C $\geq 6.5\%$

OR

- Random plasma glucose greater than or equal to 200 AND symptoms of hyperglycemia or hyperglycemic crisis
 - What are symptoms of hyperglycemia?

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

Guidelines



- **Some recent guidelines**

- **Diabetes**

- ✦ **2017**

- American College of Physicians- Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practical Guideline Update from the American College of Physicians.
- American Diabetes Association-Standards of Medical Care in Diabetes

- ✦ **2015**

- American Association of Clinical Endocrinologists and American College of Endocrinology- Clinical Practice Guidelines for Developing A Diabetes Mellitus Comprehensive Care Plan

- **Obesity**

- ✦ **2016**

- American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Comprehensive Medical Care of Patients with Obesity- Executive Summary

- ✦ **2015**

- The Endocrine Society-Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline

- ✦ **2013**

- American Heart Association/American College of Cardiology/The Obesity Society-Guideline for the Management of Overweight and Obesity in Adults

Pharmacologic Therapy For DM Type 2



- Oral agents
 - Biguanides
 - ✦ Metformin
 - Sulfonylureas
 - ✦ Glyburide
 - ✦ Glipizide
 - ✦ Glimepiride
 - Meglitinides
 - ✦ Repaglinide
 - ✦ Nateglinide
 - Thiazolidinediones
 - ✦ Pioglitazone
 - ✦ Rosiglitazone

Pharmacologic Therapy for DM Type 2



- Oral agents
 - DPP-4 inhibitors
 - ✦ Sitagliptin
 - ✦ Saxagliptin
 - ✦ Linagliptin
 - ✦ Alogliptin
 - Alpha-glucosidase inhibitors
 - ✦ Acarbose
 - ✦ Miglitol
 - Bile acid sequestrant
 - ✦ Colesevelam
 - Sodium glucose co-transporter 2 (SGLT2) inhibitors
 - ✦ Canagliflozin
 - ✦ Dapagliflozin
 - ✦ Empagliflozin
 - Dopamine-2 agonist
 - ✦ Bromocriptine

Pharmacologic Therapy for DM Type 2



- **Injectable agents**
 - **GLP-1 Agonists**
 - ✦ Exenatide
 - ✦ Exenatide extended release
 - ✦ Liraglutide
 - ✦ Abliglutide
 - ✦ Dulaglutide
 - ✦ Lixisenatide
 - **Amylin analog**
 - ✦ Pramlintide
 - **Insulin (see next slide)**

Pharmacologic Therapy for DM Type 2



- **Insulin**
 - Rapid acting analogs
 - ✦ Lispro
 - ✦ Aspart
 - ✦ Glulisine
 - ✦ Inhaled
 - Short acting
 - ✦ Human Regular
 - Intermediate acting
 - ✦ Human NPH
 - Concentrated Human Regular Insulin
 - ✦ U-500 Human Regular insulin
 - Basal analogs
 - ✦ Glargine
 - ✦ Detemir
 - ✦ Degludec
 - Mix insulin
 - ✦ 70% NPH and 30% regular
 - ✦ 50% insulin lispro protamine and 50% insulin lispro
 - ✦ 75% insulin lispro protamine and 25% insulin lispro
 - ✦ 70% insulin aspart protamine and 30% insulin aspart

Oral Agents



- In the news:
 - Metformin
 - ✦ Changes to labeling
 - ✦ Periodic measurement of B12 levels (and supplementation as needed) with prolonged use
 - Adverse events
 - ✦ DPP-4 inhibitors
 - ✦ SGLT-2 inhibitors

FDA LABEL CHANGES FOR METFORMIN



- Before starting metformin, obtain the patient's eGFR.
- Metformin is contraindicated in patients with an eGFR $<30\text{mL}/\text{min}/1.73\text{m}^2$.
- Starting metformin in patients with an eGFR between $30\text{--}45\text{mL}/\text{min}/1.73\text{m}^2$ is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls $<45\text{mL}/\text{min}/1.73\text{m}^2$, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls $<30\text{mL}/\text{min}/1.73\text{m}^2$.
- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between $30\text{--}60\text{mL}/\text{min}/1.73\text{m}^2$; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

Metformin-containing Drugs: Drug Safety Communication-Revised Warnings for Certain Patients with Reduced Kidney Function Posted online 4/8/2016 www.fda.gov

DPP-4 Inhibitors



- **Joint pain**
 - 2015- FDA warning that DPP-4 Inhibitors may cause joint pain that can be severe and disabling.
- **Pancreas**
 - Post marketing reports of acute pancreatitis in association with DPP-4 inhibitors.
 - Currently insufficient data to know if there is a causal relationship
 - Insufficient evidence to confirm an increased risk of pancreatic cancer. Monitoring and reporting continues.
- **Heart failure**
 - FDA warning Saxagliptan and Alogliptan
 - No causal relationship established.
 - Further studies...

SGLT-2 Inhibitors



- Reports of:
 - “Euglycemic” DKA
 - More frequent bone fractures-Canagliflozin
 - Increase in leg and foot amputations-Canagliflozin

Types of Insulin



- **Rapid** acting (analogues)

- Lispro
- Aspart
- Glulisine

- **Short** acting (human)

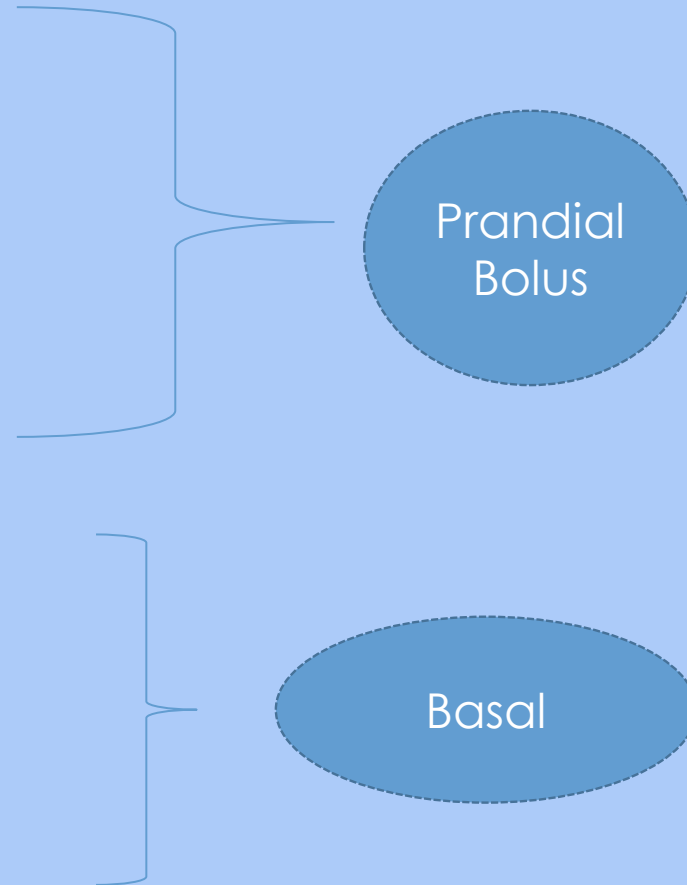
- Regular

- **Intermediate** acting (human)

- NPH

- **Long** acting (analogues)

- Glargine
- Detemir

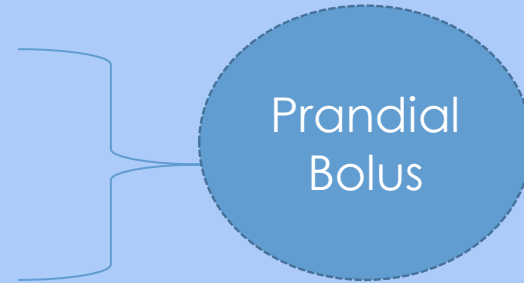


Types of Insulin



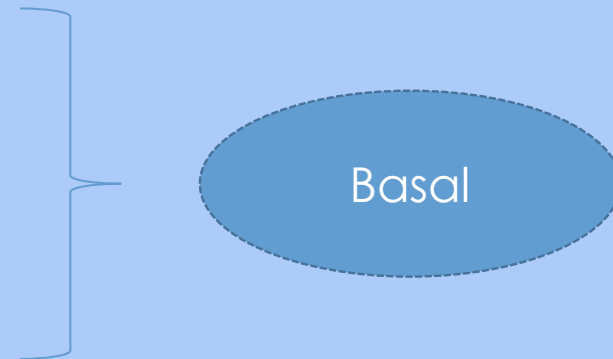
- **Rapid** acting (analogues)

- Human insulin inhalation powder



- **Ultra-long** acting (analogues)

- Degludec



Insulin



- Ultralong acting insulin
- Concentrated insulin

Degludec



- **Ultralong acting basal insulin**
 - $1/2$ life ~25 hours
 - Duration of action >42 hours
 - Glucose lowering effect is evenly distributed over 24 hour dosing interval

New Agents



- Combination insulin and GLP-1 agonist

New Technology



- FreeStyle Libre Pro System
 - FDA approved for use *by physicians* for monitoring glucose in patient with diabetes

What is your approach?



- Motivational interviewing
- Anticipatory guidance
- Patient centered care

Risk factors for DM



- Physical inactivity
- First degree relative with diabetes
- High risk race/ethnicity
 - African American, Latino, Native American, Pacific Islander, Asian American
- Women who were diagnosed with GDM
- History of CVD
- Hypertension (BP $\geq 140/90$ or on treatment for HTN)
- HDL < 35 and/or Triglycerides > 250
- A1C $\geq 5.7\%$, IFG, or IGT on prior testing
- Women with polycystic ovarian syndrome
- Other clinical conditions associated with insulin resistance
 - Severe obesity, acanthosis nigricans

What are the categories of increased risk for diabetes (prediabetes)?



- Impaired fasting glucose (IFG) 100-125 mg/dl
- OR**
- Impaired glucose tolerance (IGT) 2 hour plasma glucose in 75 g OGTT 140-199 mg/dl
- OR**
- HbA1C 5.7-6.4%

Diabetes Prevention Program (DPP)



- Participants-overweight with prediabetes
- Randomly assigned:
 - Placebo
 - Metformin 850 mg twice daily
 - Lifestyle modification program
 - ✦ At least 7 percent weight loss
 - ✦ At least 150 minutes of physical activity per week
- Results:
 - Compared with placebo
 - ✦ Lifestyle intervention reduced incidence of diabetes by 58%
 - ✦ Metformin reduced incidence of diabetes by 31%
- Conclusions:
 - Lifestyle changes and metformin both reduced incidence of diabetes in persons at high risk.
 - Lifestyle interventions were more effective than metformin.

Is it sustainable?



- DPP reduced incidence over three years
- Other studies of lifestyle intervention for diabetes prevention have shown sustained reduction in the rate of conversion to type 2 diabetes
 - DaQing study
 - ✦ 43% reduction at 20 years
 - Finnish Diabetes Prevention Study (DPS)
 - ✦ 43% reduction at 7 years
 - U.S. Diabetes Prevention Program Outcomes Study (DPPOS)
 - ✦ 34% reduction at 10 years

American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1):S1-S35.

Khavandi, K., Amer, H., Ibrahim, B., Brownrigg, J. (2013) Strategies for preventing type 2 diabetes: an update for clinicians. *Therapeutic Advances in Chronic Disease*. 4(5):242-261.

Management of Prediabetes



- Preferred treatment approach is intensive lifestyle management
 - Medical nutrition therapy
 - Appropriately prescribed physical activity
 - Avoidance of tobacco products
 - Adequate quantity and quality of sleep
 - Limited alcohol consumption
 - Stress reduction

How to prevent/delay DM Type 2?



- Patients with IGT, IFG or HgbA1C 5.7-6.4%
 - Refer to effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150 min/week moderate activity
- Metformin may be considered in those at highest risk for developing DM Type 2
 - *Off label use-not FDA approved for Type 2 DM prevention*
- Follow-up counseling should be provided and monitoring of labwork
- Screening for and treatment of modifiable CVD risk factors
- Diabetes self management and support programs
- Use of technology

Weight Loss



- Modest persistent weight loss
 - Can delay progression from prediabetes to Type 2 diabetes

Weight Loss



- Modest weight loss (defined as sustained reduction of 5% of initial body weight) in overweight and obese patients with DM Type 2
 - Improves glycemic control
 - Reduces need for glucose lowering medications

What is the role of pharmacology in preventing DM Type 2?



- **What have the studies shown?**
 - Antidiabetic medications
 - Antihypertensive medications
 - Weight loss medications

Metabolic Surgery



- **Bariatric surgery**
 - Data supporting treatment of DM Type 2
 - No randomized studies of prevention of Type 2 DM in obese patients without Type 2 DM
 - ✦ Swedish Obese Subjects Trial
 - Nonrandomized study-surgically treated patients have reduced risk of progression to DM Type 2 for up to 15 years



- “The diabetic who know the most lives the longest.”
 - Elliot P. Joslin, M.D.

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