Diabetes Prevention & Metabolic Syndrome

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Presenter Financial Relationships Disclosure

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Speaker’s Bureau: Sanofi

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Learning Objectives

- Discuss the relationship of **metabolic syndrome** and **chronic disease**
- Discuss **laboratory findings** associated with metabolic syndrome
- Discuss the criteria for screening for **prediabetes** and defining prediabetes
- Discuss the development and implementation of a **management plan** to proactively evaluate patients with prediabetes
- Discuss the **clinical evidence** used to support the management of individuals with prediabetes

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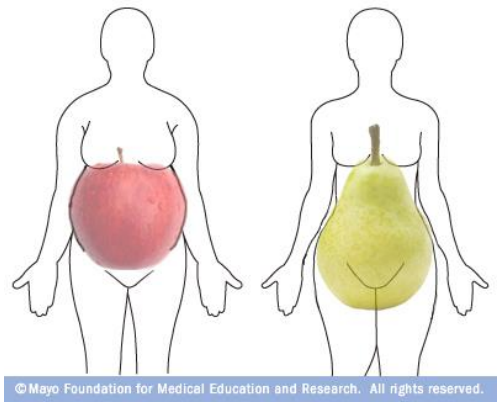
Metabolic Syndrome

- Risk factors occurring together that increase the risk for cardiovascular disease, stroke, type 2 diabetes and cancer
- Central Obesity and insulin resistance-most importance underlying factors of the syndrome
- Referred to as:
  - Dysmetabolic syndrome
  - Hypertriglyceridemic waist
  - Obesity syndrome
  - Metabolic syndrome X
  - Syndrome X
  - Cardiometabolic syndrome
  - Deadly Quartet
  - Insulin resistance syndrome



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Metabolic Syndrome

- Risk for heart disease, diabetes, and stroke increases with the number of metabolic risk factors
- Risk is linked to overweight and obesity and a lack of physical activity
- Insulin resistance increases risk
- Becoming more common due to a rise in obesity rates among adults
- In the future, may overtake smoking as the leading risk factor for heart disease

Metabolic Syndrome

Local Metabolic Abnormalities	Systemic Metabolic Abnormalities	Systemic Disease
• **Adipose Tissue** • Liver • Skeletal Muscle • Pancreas • CNS	• **Metabolic Syndrome** • Visceral Obesity • Insulin Resistance • Glucose Intolerance • Dyslipidemia • Hypertension	• **Human Disease** • Cardiovascular Disease • Liver Disease • Diabetes • Cancer • Other

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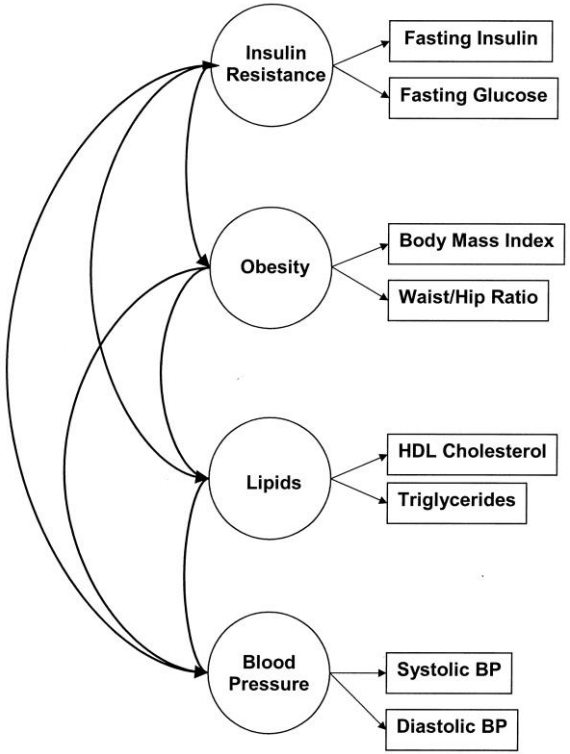
Pathogenesis

Factor structure of the metabolic syndrome.



Richard Kahn et al. Dia Care 2005;28:2289-2304

Metabolic Syndrome

- Multiple definitions
  - World Heath Organization
  - European Group for the Study of Insulin Resistance
  - National Cholesterol Education Program ATP III
  - American Association of Clinical Endocrinologists
  - International Diabetes Federation
  - American Heart Association & National Heart, Lung and Blood Institute (NHLBI)

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Metabolic Syndrome: NCEP ATP III

Defined by three or more of the following criteria:

- Abdominal obesity: WC ≥102 cm in men and ≥88 cm in women
- Hypertriglyceridemia: ≥150 mg/dl (1.695 mmol/l)
- Low HDL-C: <40 mg/dl in men and <50 mg/dl in women
- High blood pressure (BP): >130/85 mmHg
- High fasting glucose: >100 mg/dl

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)

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Metabolic Syndrome: WHO

Glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus (DM), and/or insulin resistance, together with two or more of the components listed below:

- Raised arterial pressure, i.e., ≥140/90 mm of Hg
- Raised plasma triglyceride (≥ 150 mg/dl) and/or low HDL-C (<35 mg/dl in men and <39 mg/dl in women)
- Central obesity, i.e., waist/hip ratio (WHR) >0.9 in men and >0.85 in women and/or body mass index (BMI) >30 kg/m^2
- Microalbuminuria, i.e., urinary albumin excretion rate ≥ 20 µgm/minute or albumin/creatinine ratio ≥ 30 µgm/mg

World Health Organization (WHO)

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Central Obesity/Intra-abdominal Adiposity (IAA)

- Potential to influence metabolism and cardiometabolic risk
  - Alterations in secretion of adipokines
- Adiponectin, a cardioprotective adipokine
  - Reduced in abdominally obese individuals
- IAA promotes increased secretion of metabolites and biologically active substances
  - Glycerol
  - Free fatty acids (FFA)
  - Inflammatory mediators [e.g., tumor necrosis factor alpha (TNFa), interleukin-6 (IL-6)]
  - Plasminogen activator inhibitor-1 (PAI-1)
  - C-reactive protein (CRP)

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Central Obesity and Inflammatory Risk

- **Vascular dysfunction**
  - Endothelial dysfunction
  - Microalbuminuria
- **Pro-inflammatory state**
  - Elevated CRP
  - Elevated inflammatory cytokines (TNF-α, IL-6)
  - Decreased adiponectin levels
- **Pro-thrombotic state**
  - Increased anti-fibrinolytic factors (PAI-1)
  - Increased fibrinogen

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Associating Risk

- Sedentary/Inactive lifestyle
- Consumption of high-calorie, low-fiber fast foods
- Populations
  - People who have a personal history of diabetes
  - People who have a sibling or parent with diabetes
  - Women when compared with men
  - Women who have a personal history of polycystic ovarian syndrome
  - Mexican Americans (highest rate), followed by whites and blacks

Low Fiber

Sedentary

High Calorie

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Associating Risk

- The risk for serious health concerns such as coronary artery disease, hypertension, dyslipidemia, albuminuria, and a range of other conditions increases with increased Body Mass Index (BMI)
- Obesity is most commonly assessed by the BMI
  - Individuals with a BMI between 25 and 29.9 are considered overweight
  - Individuals with a BMI of 30 and above are considered obese

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Associating Risk
Body Mass Index vs Waist Circumference

- Body Mass Index
  - Incorporates height and weight
  - Does not incorporate body composition (difference between excess fat and muscle, fat distribution), fitness, age, race, or gender
- Waist Circumference
  - More highly correlated with metabolic risk factors
  - NCEP ATP III
    - Men > 40 inches
    - Women >35 inches

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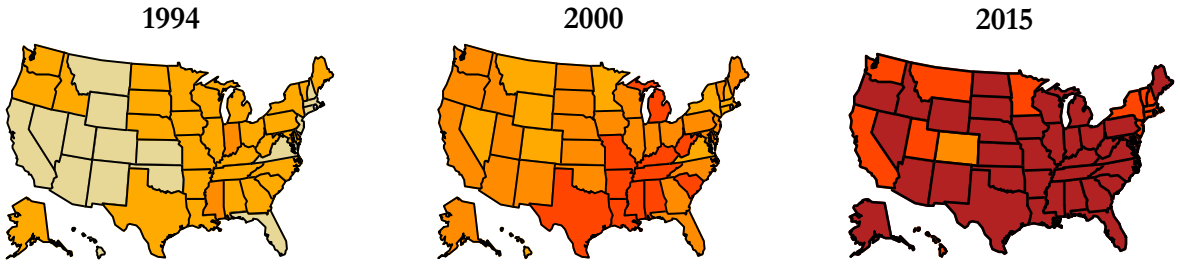
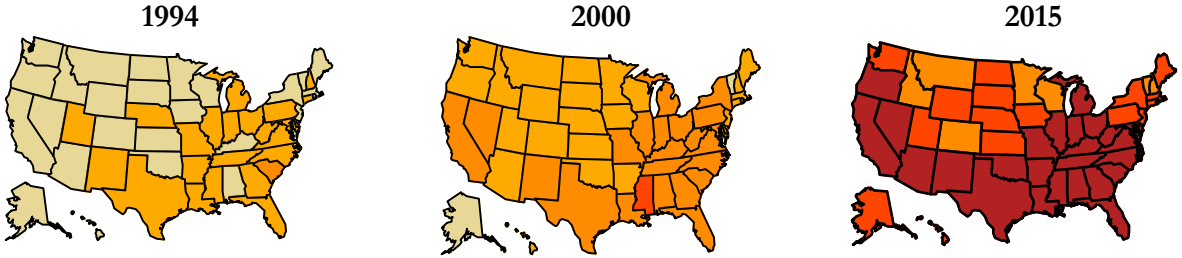
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI ≥30 kg/m²)



No Data <14.0% 14.0%–17.9% 18.0%–21.9% 22.0%–25.9% ≥ 26.0%

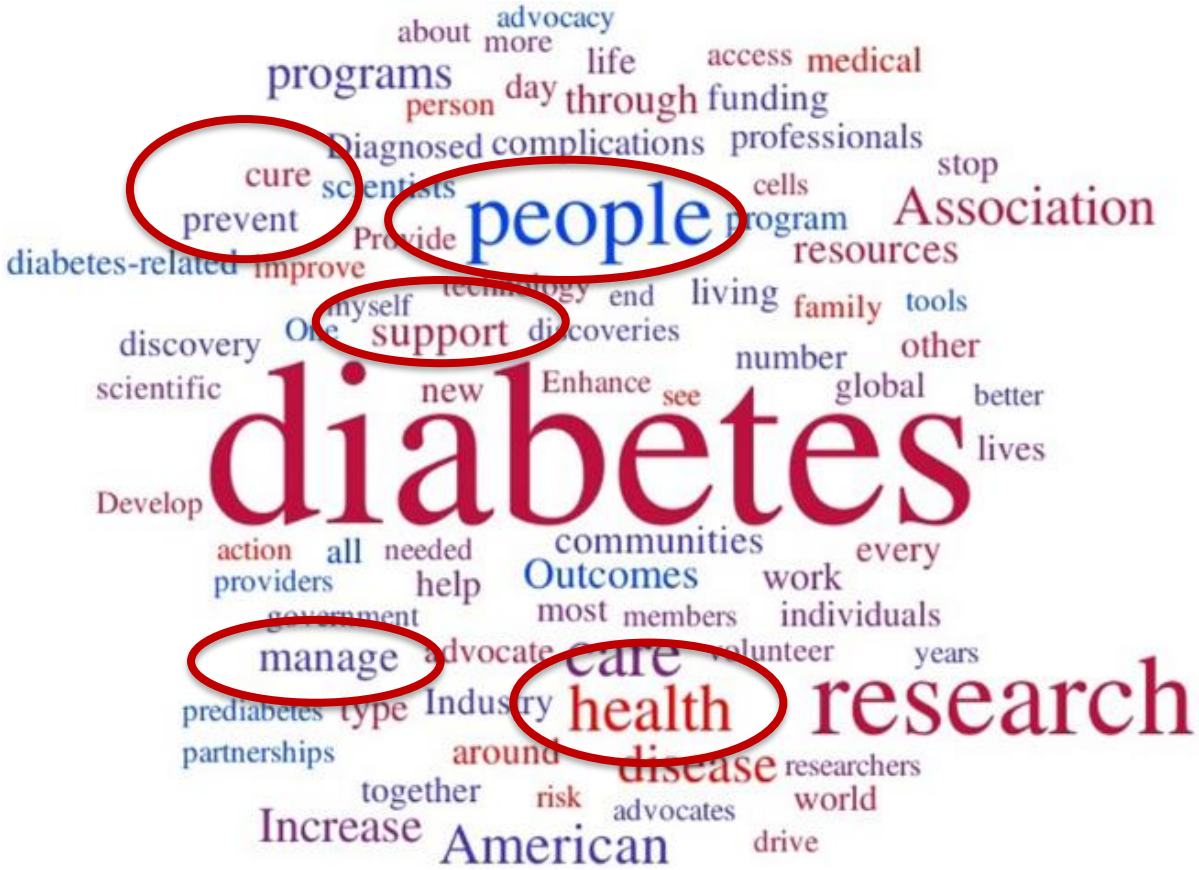
Diabetes



No Data <4.5% 4.5%–5.9% 6.0%–7.4% 7.5%–8.9% ≥9.0%

Obesity and Diabetes

CDC's Division of Diabetes Translation. United States Surveillance System available at http://www.cdc.gov/diabetes/data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years
prediabetes
type
Industry
health
research
partnerships
around
disease
researchers
together
risk
advocates
world
Increase
American
drive

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Prevalence of Diabetes in the United States

National Diabetes Statistics Reports, 2017

- Estimates of Diabetes and its Burden in the United States
- Centers from Disease Control and Prevention

Diabetes

- 30.3 million (9.4%)
- 23.1 million diagnosed
- 7.2 million undiagnosed
- 23.8% have Diabetes—but do not know it!

Prediabetes

- 84.1 million (18+ years old)
- 33.9% of U.S. population
- 65+ years: 23.1 million

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Prediabetes

- Epidemiologic evidence suggests that the **complications** of type 2 diabetes begin early in the progression from NGT to frank diabetes
- Prediabetes and diabetes are conditions in which **early detection** is appropriate, because
  - Duration of hyperglycemia is a predictor of **adverse outcomes**
  - There are effective interventions to **prevent disease progression** and to reduce complications

NGT, normal glucose tolerance ; T2D, type 2 diabetes

Garber AJ, et al. *Endocr Pract*. 2008;14:933-946

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Feasibility of Preventing Type 2 Diabetes

- There is a long period of **glucose intolerance** that precedes the development of diabetes
- Screening tests can identify **persons at high risk**
- There are safe, potentially effective interventions that can address **modifiable risk factors**:
  - Obesity
  - Body fat distribution
  - Physical inactivity
  - High blood glucose

Prediabetes Risk Test

Garber AJ, et al. *Endocr Pract*. 2008;14:933-946

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AACE Prediabetes Consensus Statement

- Untreated individuals with prediabetes are at increased risk for diabetes as well as for **microvascular and macrovascular complications**
- Treatment goals are to prevent deterioration in **glucose levels** and modify **other risk factors** such as obesity, hypertension, and dyslipidemia
  - The same blood pressure and lipid goals are suggested for prediabetes and diabetes
- Intensive **lifestyle management** is the cornerstone of all prevention efforts; pharmacotherapy targeted at glucose may be considered in high-risk patients

21 Handelsman YH, et al. *Endocr Pract*. 2015;21(suppl 1):1-87
Garber AJ, et al. *Endocr Pract*. 2008;14:933-946

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Policy Paradigm Shifts are Needed to Stem the Global Tide of Type 2 Diabetes

- Integrating **primary and secondary prevention** along a clinical continuum
- **Early detection** of prediabetes and undiagnosed diabetes
- Implementing **cost-effective prevention** and control by integrating community and clinical expertise and resources within affordable service delivery systems
- Sharing and adopting **evidence-based policies** at the global level

T2D, type 2 diabetes

Narayan KM, et al. *Health Aff (Millwood)*. 2012;31:84-92

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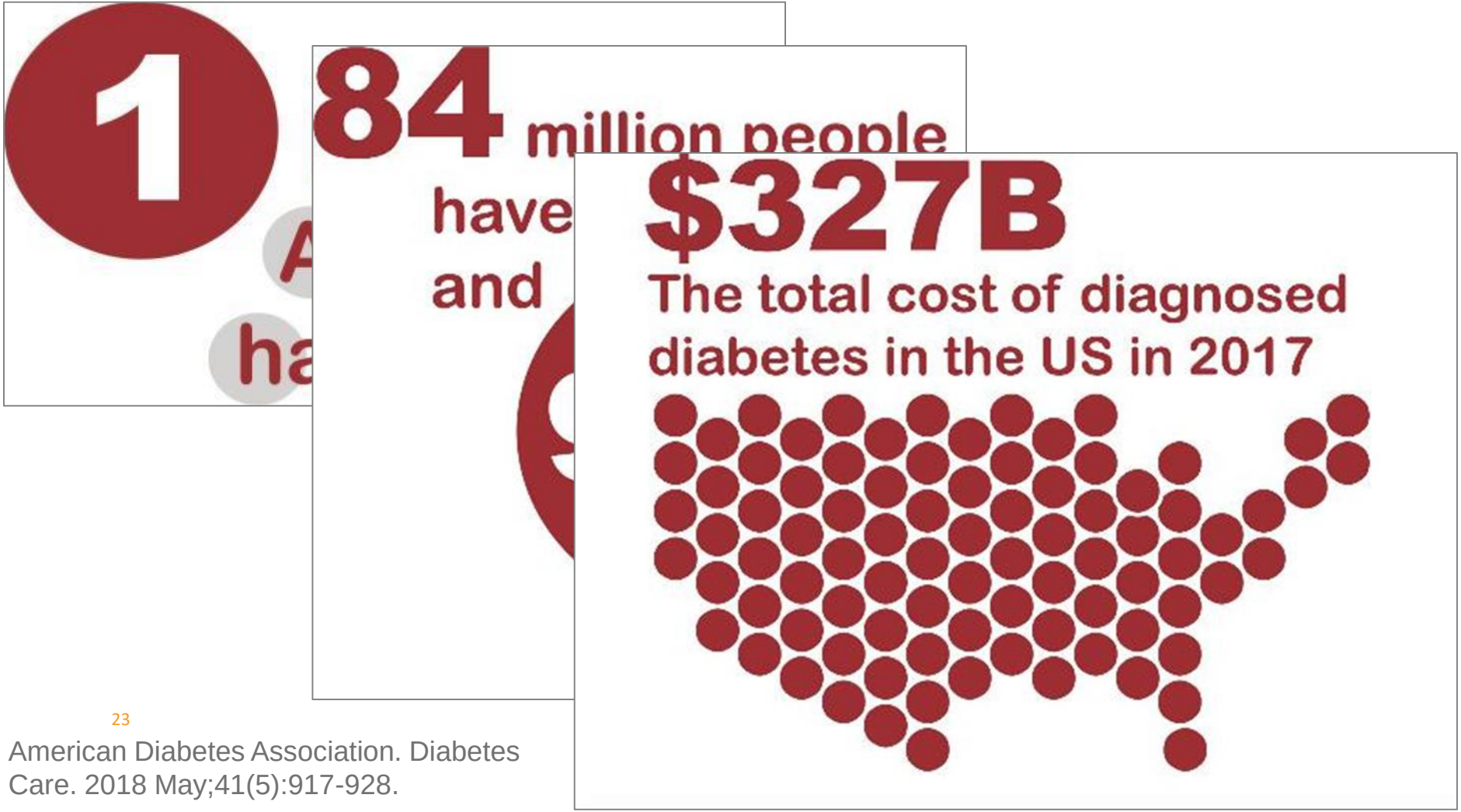

American Diabetes Association. Diabetes Care. 2018 May;41(5):917-928.

Interventions to Reduce Risks Associated with Prediabetes

- **Therapeutic lifestyle** management is the cornerstone of all prevention efforts
- **No pharmacologic agents** are currently approved for the management of prediabetes
  - Pharmacotherapy targeted at glucose may be considered in high-risk patients after individual risk-benefit analysis

Garber AJ, et al. *Endocr Pract*. 2008;14:933-946

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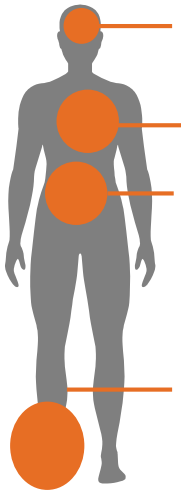
Staggering Health Burden of Diabetes in the US: The Diabetes Crisis in Contemporary Context of Another Health Crisis

IN THE US, Diabetes CONTRIBUTES TO ON AVERAGE[1]:



1 stroke every
2 minutes

1 case of ischemic heart disease
80 seconds

1 case of kidney failure every
10 minutes

1 lower limb amputation every
5 minutes

In the US, 1 PERSON DIES EVERY 6½ MINUTES FROM DIABETES AND ITS COMPLICATIONS[2]

That's more than
218 people a day

IN THE UNITED STATES, IN 2016, 1 PERSON DIES EVERY 52 MINUTES FROM OPIOD OVERDOSE[3]

That's more than
46 people a day

Type 1 or Type 2 Diabetes

1. CDC. *National Diabetes Statistics Report 2017*. www.cdc.gov/statistics. 2. IDF Diabetes Atlas, 8th edition. 2017

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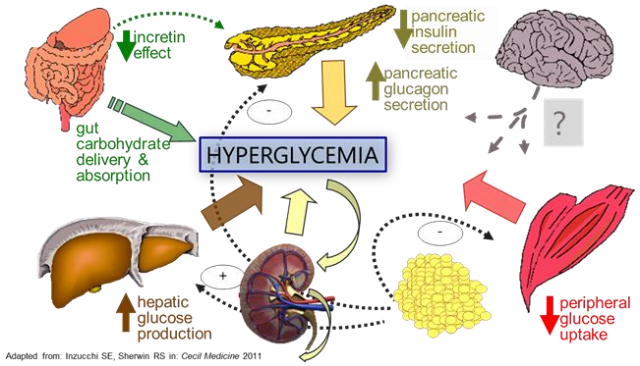
Therapeutic Advances Over the Past 20 Years



ADA Standards of Care 1989

SGLT-2 Inhibitor
Bromocriptine
DPP-4 inhibitor
Pramlintide
GLP-1R agonist
Meglitinide
TZD
Basal insulin
Rapid-acting insulin
αGlucosidase inhibitor
Metformin
Insulin
SFU

1920 1960 1970 1980 1990 2000 2010 2014

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Despite the Advancement and Investment we are Not Achieving our Goals

- **Decline in %** of patients at **HbA1c <7%**
- At best, only about **50%** of patients are at **goal**
- **Increase in %** of patients with **very poor control**
- Unacceptable level of **morbidity** and **mortality**
- Diabetes-related **costs** to society are tremendous

ALL THIS DESPITE MORE THAN 40 NEW T2D TREATMENT OPTIONS APPROVED SINCE 2005

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Carls G . Huynh J . Tuttle *et al*. Achievement of Glycated Hemoglobin Goals in the US Remains Unchanged Through 2014. Diabetes Ther 2017;8:863–873

Cardiovascular (CV) Risk Factor Targets and CV Disease Event Risk in Diabetes:

We are not getting the job done

Percent at target levels for any one, two, or all three factors among the 2018 persons with diabetes:

Any 1 of 3	Any 2 of 3	3 of 3
41.1%	26.5%	7.2%

Percent CVD risk reduction for being at target level among the 2018 persons with diabetes for each of the measures:

Blood pressure	LDL-C	HBA1c
17%	33%	37%

Percent lower adjusted risk of CVD events with one, two, or three risk factors at target level:

Any 1 of 3	Any 2 of 3	3 of 3
36%	52%	62%

Wong, et al. Diabetes Care 2016 May; 39(5) 668-676.

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Lifestyle Intervention in Prediabetes

- Persons with prediabetes should **reduce weight by 5% to 10%**, with long-term maintenance at this level
  - A program of regular **moderate-intensity physical** activity for 30-60 minutes daily, at least 5 days a week, is recommended
  - A diet that includes **caloric restriction**, **increased fiber** intake, and (in some cases) **carbohydrate intake limitations** is advised

Garber AJ, et al. *Endocr Pract*. 2008;14:933-946
Garber AL, et al. *Endocr Pract*. 2017;23:207-238

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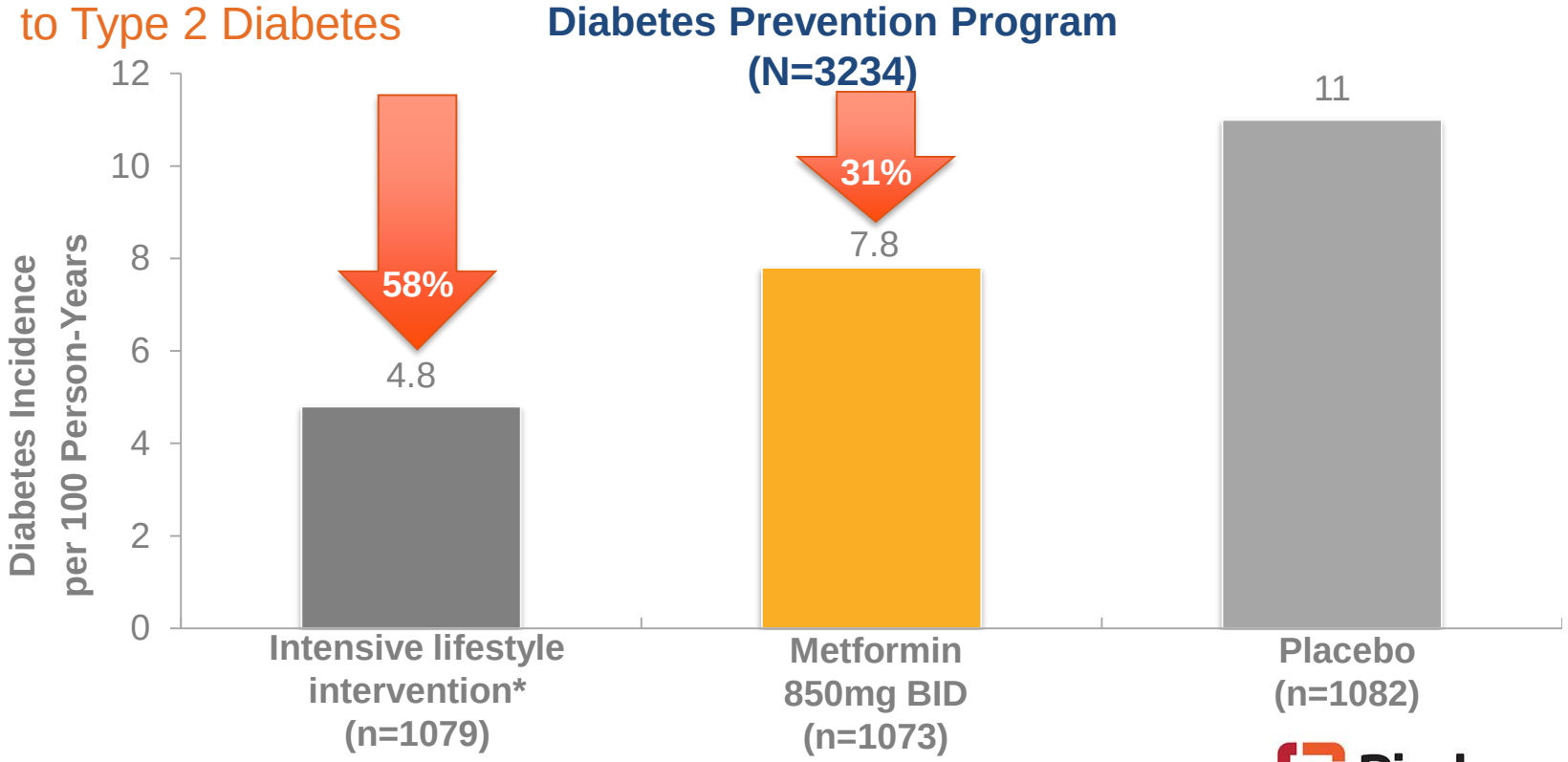
Intensive Lifestyle Intervention Effectively Prevents Progression from IGT to Type 2 Diabetes



IGT, impaired glucose tolerance; T2D, type 2 diabetes

DPP Research Group. *N Engl J Med*. 2002;346:393-403

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise

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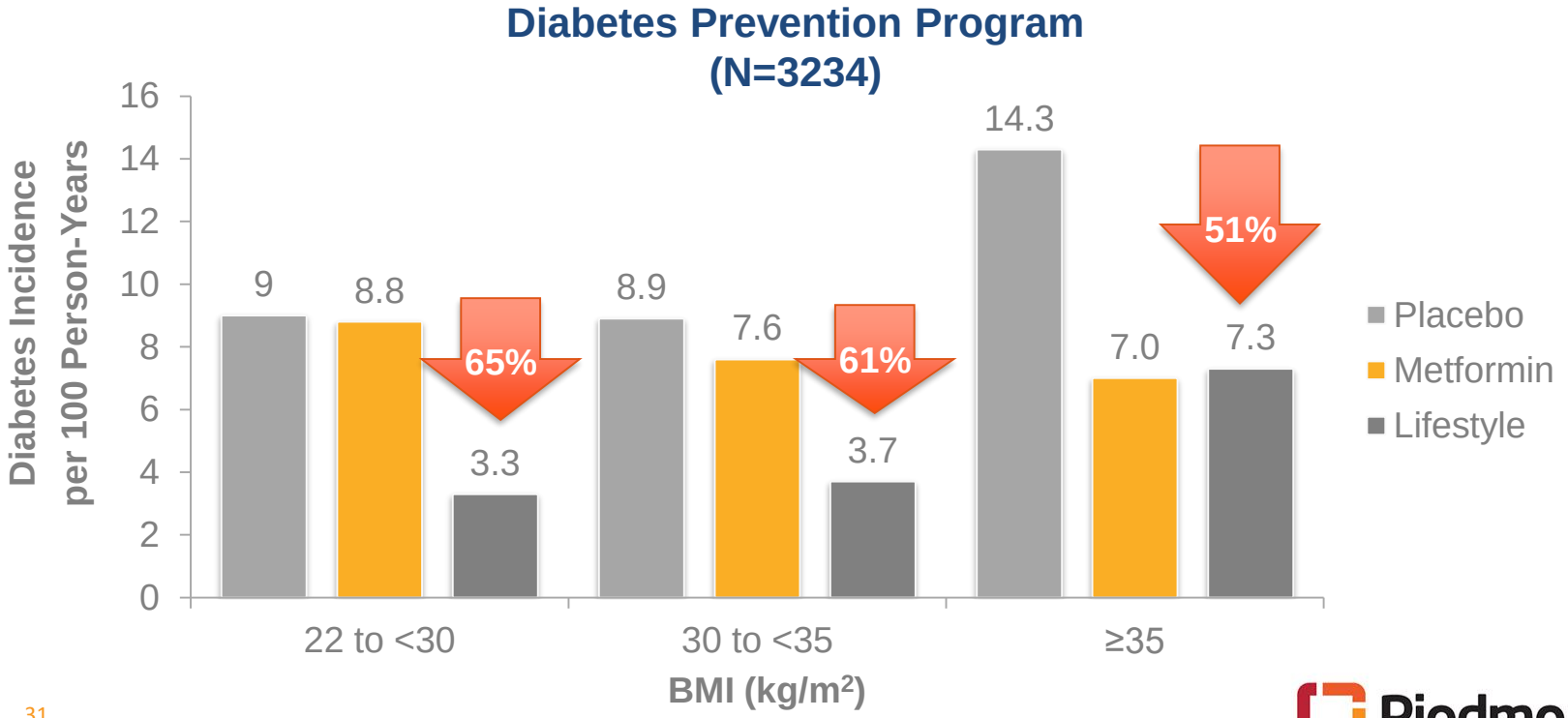
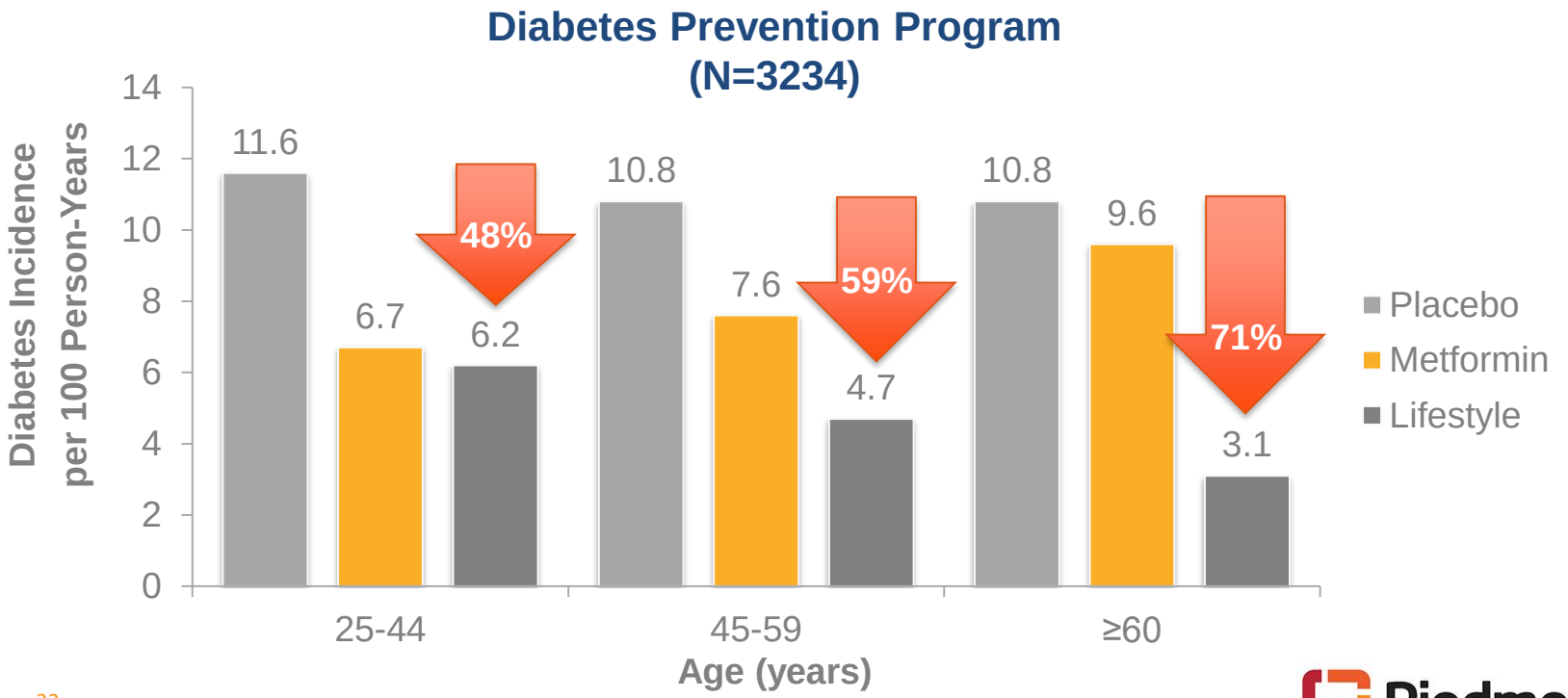
Effectiveness of Lifestyle Intervention for Diabetes Prevention Wanes as Weight Increases



DPP Research Group. *N Engl J Med*. 2002;346:393-403

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise

Lifestyle Intervention More Effectively Prevents Diabetes as Populations Age



DPP Research Group. *N Engl J Med*. 2002;346:393-403

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise

Medical and Surgical Interventions Shown to Delay or Prevent T2D

Intervention	Follow-up Period	Reduction in Risk of T2D (P value vs placebo)
Antihyperglycemic agents		
Metformin[1]	2.8 years	31% ($P<0.001$)
Acarbose[2]	3.3 years	25% ($P=0.0015$)
Pioglitazone[3]	2.4 years	72% ($P<0.001$)
Rosiglitazone[4]	3.0 years	60% ($P<0.0001$)
Weight loss interventions		
Orlistat[5]	4 years	37% ($P=0.0032$)
Phentermine/topiramate[6]	2 years	79% ($P<0.05$)
Bariatric surgery[7]	10 years	75% ($P<0.001$)

T2D, type 2 diabetes

1. DPP Research Group. *N Engl J Med*. 2002;346:393-403. 2. STOP-NIDDM Trial Research Group. *Lancet*. 2002;359:2072-2077
3. Defronzo RA, et al. *N Engl J Med.* 2011;364:1104-15. 4. DREAM Trial Investigators. *Lancet*. 2006;368:1096-1105
5. Torgerson JS, et al. *Diabetes Care*. 2004;27:155-161. 6. Garvey WT, et al. *Diabetes Care*. 2014;37:912-921
7. Sjostrom L, et al. *N Engl J Med*. 2004;351:2683-2693

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Calorie Restriction

Lowers HbA1c in proportion to weight lost

9kg loss lowers HbA1c by about 0.9%*

Other Benefits

- Potential **remission of DM**
  - 46% at 1 year in DIRECT food substitution diet
- Reduction of **ASCVD risk factors**
- Reduction in use of **glucose-lowering drugs**
- Proven **safety**

An **individualized MNT** should be offered to all patients

All overweight and obese patients with diabetes should be advised of the health benefits of weight loss and encouraged to engage in a program of intensive **lifestyle management**, which may include food substitution

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Physical Activity

- **Lowers HbA1c** by about **0.6%**
- More is better
- **Supervised exercise** more effective than unsupervised
- Exercise has other health benefits
  - Reduction of ASCVD risk factors
  - Reduction of fall risk
  - Reduction of weight
  - Increase bone density

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Relationship of Walking to Mortality Among US Adults with Diabetes

- DESIGN: Prospective cohort study
- SUBJECTS: 2896 adults,1990 and 1991 National Health Interview Survey
- RESULTS:

Mortality	Inactive	2 hours/wk	3-4 hours/wk
All Cause	Ref 1.0	↓39%	↓54%
CV	Ref 1.0	↓34%	↓53%

CONCLUSIONS: **Walking** was associated with lower mortality across a diverse spectrum of adults with diabetes. One death per year may be preventable for every 61 people who could be persuaded to **walk at least 2 h/wk**.

Arch Intern Med. 2003 Jun 23;163(12):1440-7

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Guidelines are Tools

- As a medical community our goal is to **improve patient outcomes**
- Evidence-based guidelines should assist the PCP and the patient in **shared decision making**
- The essence of the ADA-EASD Consensus statement on Management of Hyperglycemia is a focus on **patient factors** and **preferences** and the ever increasing choice of therapies available for glucose control
- The goals of diabetes care are to prevent short-term and long-term complications and optimize **quality of life**

Complex guidance leaves the PCP and the patient with a lot of work!

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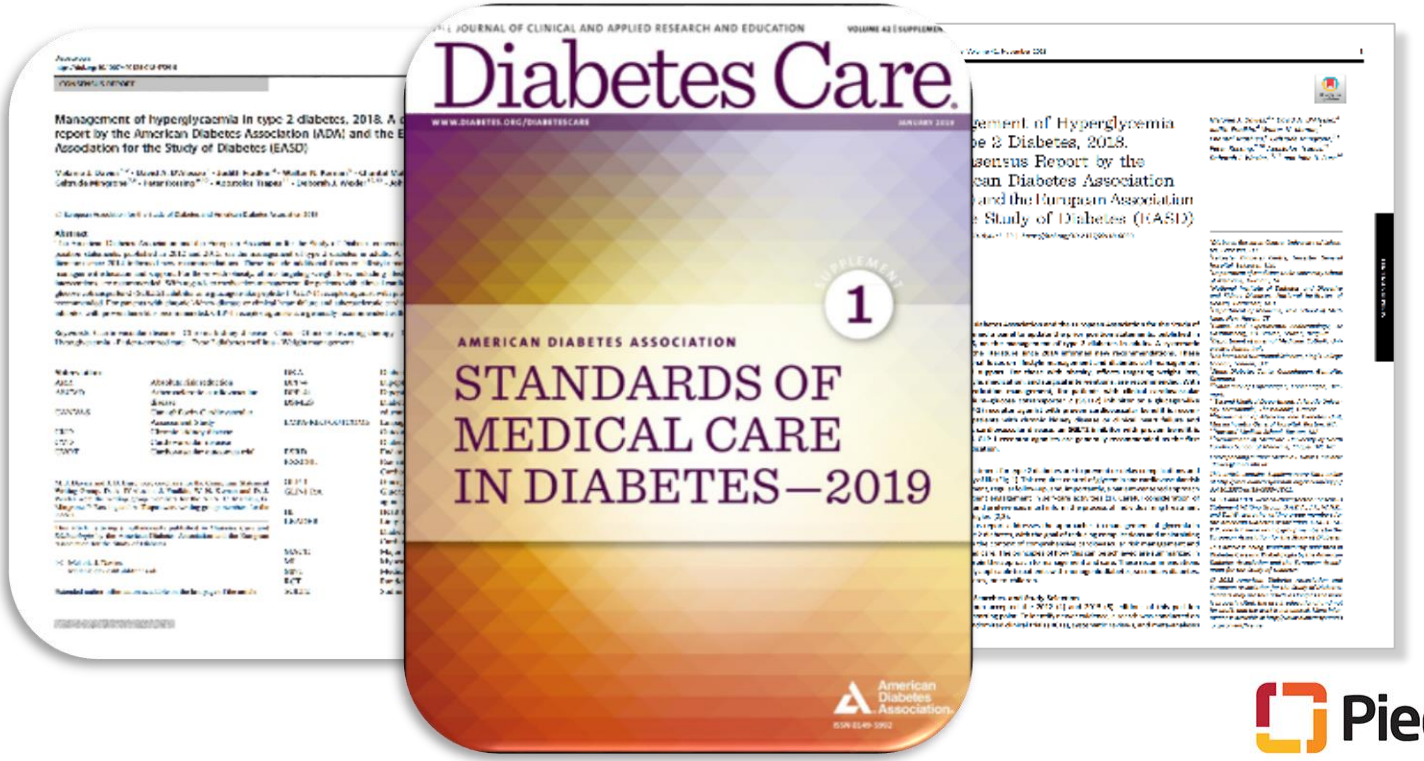
Consensus Report

Diabetologia https://doi.org/10.1007/s00125-018-4729-5



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Diabetes Care 2018;41:1-33 https//:doi.org/10.2337/dci18-0033

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

WEIGHT LOSS THERAPIES

TREAT HYPERGLYCEMIA
FPG > 100 | 2-hour PG > 140

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO HYPERGLYCEMIA ALGORITHM

1 PRE-DM CRITERION

Intensify Weight Loss Therapies

MULTIPLE PRE-DM CRITERIA

Low-risk Medications
- Metformin
- Acarbose

Consider with Caution
- TZD
- GLP-1 RA

If glycemia not normalized

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

 DOI 10.4158/EP161682.CS

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Summary

Lifestyle is the foundation*

- Highly effective in motivated, adherent patients

Medications

- Lots of choices
- We hope to make it easier to navigate them
- Safety, efficacy, cost and convenience

Metabolic surgery*

- Consider it as very effective salvage therapy

*The only choices that can lead to disease remission

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Lifestyle Take Home Points

- Diet and Exercise are **the cornerstones** of successful diabetes management (on or off medication)
- People with diabetes and the providers **need skills** to implement sustainable lifestyle intervention
- **Provider silence on lifestyle in unacceptable**
- Patient support in the form of diabetes self management education is crucial **(early and often)**
- If at first you don't succeed-try something else!

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Points for Discussion

- **Diabetes Prevention and Remission**
  - Diet and Obesity Treatment: What are the barriers?
- **Support for Sustainable Effective Behavior Change**
  - Who should orchestrate and how can it be supported?
- **Comprehensive CVD Risk Management**
  - Who should orchestrate?
- **Guideline Harmonization: Who are we serving?**

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