

## Controversies in Primary Care: Treating Pre-Diabetes

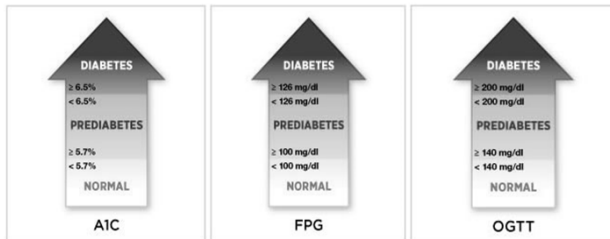
Kevin J. Goist, MD  
Assistant Professor of Clinical Medicine  
Lead Physician, GIM Inpatient Services  
Division of General Internal Medicine  
The Ohio State University Wexner Medical Center

## Disclosures

- I have no disclosures regarding the content of this lecture today.

## What is Pre-Diabetes?

- American Diabetes Association:
  - Hemoglobin A1c 5.7-6.4%
  - Fasting Plasma Glucose 100-125mg/dL
  - Two hour oral glucose tolerance test 140-199mg/dL

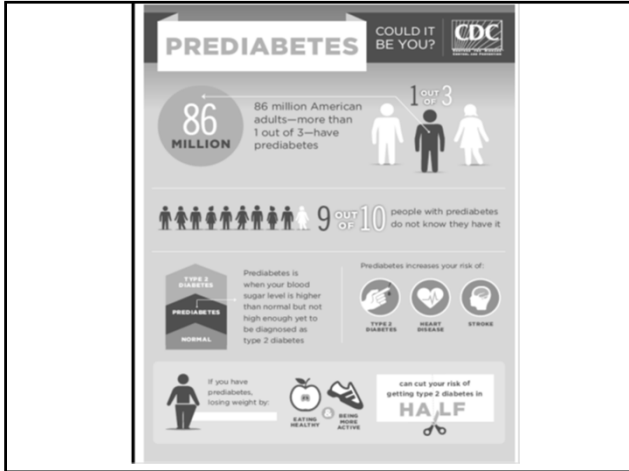


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## Pre-Diabetes: The Statistics

- 2012 CDC estimate: 86 million U.S. adults
- 11% of those adults were aware
- 15-30% develop Type 2 Diabetes in 5 years
- 50% develop Type 2 Diabetes in 10 years
- 1.5 times the risk of cardiovascular disease





- ## IGT, IFG, A1c
- **IGT**
    - Diagnosed with two hour OGTT
    - Predominantly insulin resistance in muscle tissue
    - No association with microvascular complications
    - Annual conversion to T2DM 4-6%
  - **IFG**
    - Originally defined as 110-125mg/dl
    - Changed to 100-125mg/dl in 2003
  - **Hemoglobin A1c**

## Metabolic Syndrome

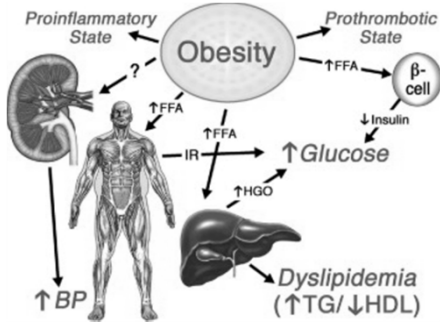
- **NCEP Definition 2001**
- **Substantial overlap with pre-diabetes**

Metabolic syndrome – NCEP ATP III criteria	
Metabolic syndrome defined as $\geq 3$ of the following NCEP ATP III criteria:	
Central obesity	Men > 102cm Women > 88cm
Blood pressure	$\geq 130 / \geq 85$ mmHg
Triglycerides	> 1.69mmol/L
HDL cholesterol	Men < 1.03mmol/L Women < 1.29mmol/L
Fasting blood glucose	> 6.1mmol/L

NCEP Expert Panel. *Circulation* 2002;106 (25):3143 - 3421

- ## Pathophysiology of Pre-Diabetes
- **Insulin resistance**
  - **Defective glucose sensing at beta cell**
  - **Relative insulin deficiency**

From: Pre-Diabetes, Metabolic Syndrome, and Cardiovascular Risk



J Am Coll Cardiol. 2012;59(7):635-643. doi:10.1016/j.jacc.2011.08.080  
Copyright © The American College of Cardiology. All rights reserved.

## Diabetes: Who do I screen?

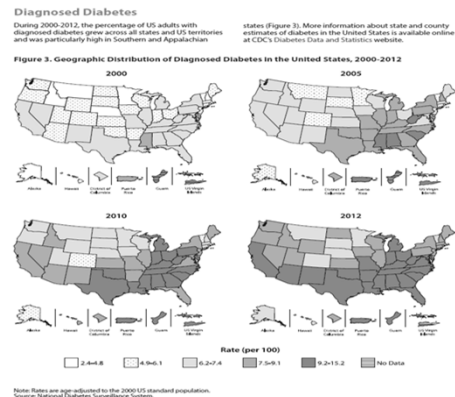
- American Diabetes Association, 2015
  - All patients at age 45, especially if obese
  - Younger adults with BMI >25kg/m<sup>2</sup> with one additional risk factor:
    - Family history of diabetes
    - Hypertension
    - Dyslipidemia
    - Sedentary lifestyle
    - Gestational diabetes/baby >9 pounds
    - High risk ethnic groups
    - Pre-diabetes
    - Cardiovascular disease

## Diabetes: Who do I screen?

- USPSTF Recommendations
  - 2015: Update in progress
    - Preliminarily:
      - Recommended for adults at increased risk
      - “Moderate net benefit”
      - “Limited evidence on harms”
  - 2008: Asymptomatic adults with sustained BP >135/80



## Why should I consider screening?



## Why should I consider screening?

- According to the USPSTF:
  - “Adequate evidence that intensive lifestyle modifications result in lower incidence of diabetes, cardiovascular mortality, and all-cause mortality.”



U.S. Preventive Services  
TASK FORCE

## Thoughts on Pre-Diabetes

M. Buysschaert and M. Bergman, 2011:

“Prediabetes (IFG and/or IGT) should be viewed as a stage in the natural history of disordered glucose metabolism rather than as a distinctive clinical entity representing an interim condition and as a risk factor presaging the development of diabetes...and an increase in cardiovascular and possibly microvascular complications.”

## Can we prevent progression to diabetes?

The New England  
Journal of Medicine

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VOLUME 346

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NUMBER 6



REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE  
INTERVENTION OR METFORMIN

DIABETES PREVENTION PROGRAM RESEARCH GROUP\*

## Diabetes Prevention Program

- 3284 patients with IGT and IFG
- Mean age 51, 68% female, mean BMI 34kg/m<sup>2</sup>
- Three treatment arms, 3 year follow up:
  - Intensive lifestyle changes
  - Metformin 850mg BID and standard lifestyle changes
  - Placebo BID and standard lifestyle changes

## Diabetes Prevention Program

- Reduction in incidence of diabetes:
  - Intensive lifestyle: 58%
  - Metformin: 31%
- Subsequent follow up study (DPPOS):
  - Intensive lifestyle: 34%
  - Metformin: 18%

## Other Prevention Recommendations

- Mediterranean Diet
  - 418 non-diabetic adults, ages 55-80, high CV risk
  - Med diets versus low fat
  - Main outcome: incidence of diabetes
    - 10.1-11% in Mediterranean Diet, 17% in low fat diet

Clinical Care/Education/Nutrition/Psychosocial Research

\*\*\*\*\*

### Reduction in the Incidence of Type 2 Diabetes With the Mediterranean Diet

Results of the PREDIMED-Reus nutrition intervention randomized trial

Diabetes Care 34:14-19, 2011

## Pharmacologic Treatment of Pre-Diabetes

- ADA Recommendations:
  - Intensive lifestyle changes for all
  - Consider Metformin for diabetes prevention in pre-DM:
    - Age <60
    - Obesity (BMI  $\geq 35\text{kg/m}^2$ )
    - History of gestational diabetes

## Pharmacologic Treatment of Pre-Diabetes

- Outside of Metformin, there is some data for:
  - Acarbose:
    - STOP-NIDDM trial
  - Pioglitazone:
    - ACT-NOW trial

Emerging Treatments and Technologies

### The STOP-NIDDM Trial

An international study on the efficacy of an  $\alpha$ -glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data

Diabetes Care 21:1720-1725, 1998

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

### Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance

Ralph A. DeFronzo, M.D., Deji Tsigally, M.D., Dawn C. Schwenke, Ph.D., Marghan Benerji, M.D., George A. Bray, M.D., Thomas A. Buchanan, M.D., Stephen C. Clement, M.D., Robert E. Henry, M.D., Howard N. Hodick, M.D., Abbas F. Khachik, M.D., Ph.D., Wendy J. Mack, Ph.D., Sander Maddala, M.D., Robert E. Ratner, M.D., Ken Williams, M.Sc., Frankie B. Stentz, Ph.D., Nicolas Musi, M.D., and Peter D. Reaven, M.D., for the ACT NOW Study

N Engl J Med 2011;364:1104-15.

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## Case #1

- Mr. J is a 51 year old man in my office for a new patient visit. He has not seen a physician “in years.” He has a BMI of 37.2kg/m<sup>2</sup> and his BP is 151/92. He reports that his father “had a heart attack when he was 53—I don’t want this to happen to me.”
- I ordered some baseline labs, including screening him for diabetes.

## Case #1

- Pertinent labs include:
  - Hemoglobin A1c: 6.3%
  - Fasting glucose: 117
  - HDL 33, LDL 132, TG 277
  - Normal renal function
- Does he warrant pharmacologic treatment to prevent diabetes, and potentially lower risk for cardiovascular disease?

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**QUARTERLY FOCUS ISSUE: PREVENTION/OUTCOMES**

Cardiovascular Risk


### Pre-Diabetes and the Risk for Cardiovascular Disease

A Systematic Review of the Evidence

Earl S. Ford, MD, MPH, Guixiang Zhao, MD, PhD, Chaoyang Li, MD, PhD

- IFG 110-125mg/dl: 18 studies, RR 0.65-2.5
  - Fixed effects summary estimate of RR 1.20
- IFG 100-125mg/dl: 8 studies, RR 0.87-1.4
  - Fixed effects summary estimate of RR 1.18
- IGT: 8 studies, RR 0.83-1.34
  - Fixed effects summary estimate of RR 1.1

## Case #1

**CLINICIAN UPDATE**  *Circulation* June 17, 2014

### Glycemic Management in Patients With Coronary Artery Disease and Prediabetes or Type 2 Diabetes Mellitus

Allison B. Goldfine, MD, Eng-Joo Poon, MBBS, Martin J. Abrahamson, MD

- **Newly-diagnosed T2DM: >50% have CAD**
- **CAD: 1/3 of patients have T2DM**
- **Screening patients with CAD without known T2DM**
  - Additional 15-20% of patients will have T2DM
  - IFG/IGT in 30-40% more

## Case #1: Treatment

- After discussion, he decided he wanted to be more aggressive with treatment
  - ACE-I for hypertension
  - HMG-CoA reductase inhibitor for hyperlipidemia
  - Metformin 850mg BID for pre-diabetes
  - Intensive lifestyle changes
  - 6 months later, A1c 5.6% and BMI is 35.2kg/m<sup>2</sup>

## Case #2

- Mrs. G is a 47 year old obese female seen in follow up in resident clinic after recent emergency department evaluation for abdominal pain. Ultrasound to assess for biliary pathology reveals hepatic steatosis. Labs most notable for ALT of 101 and AST 88.
  - Would she benefit from screening for diabetes?
  - Would she benefit from treatment if she has pre-DM?

Cardiovascular and Metabolic Risk  
ORIGINAL ARTICLE

### Prevalence of Prediabetes and Diabetes and Metabolic Profile of Patients With Nonalcoholic Fatty Liver Disease (NAFLD)

CAROLINA OTERO-LOPEZ, MD<sup>1</sup>  
ROSINA LOMONACO, MD<sup>2</sup>  
BEVERLY OREAR, BS<sup>3</sup>  
JOAN FISCH, MD<sup>3</sup>

ZHI CHENG, MD<sup>3</sup>  
VALERIA G. KOCHENOV, MD<sup>4</sup>  
JEAN HARDES, PhD<sup>5</sup>  
KENNETH CUSH, MD<sup>1,3,5</sup>

Diabetes Care 35:873–878, 2012

- 118 healthy overweight/obese subjects
- Metabolic measurements
- Magnetic resonance spectroscopy
- Oral glucose tolerance test
- Insulin sensitivity
- US-guided liver biopsy

## Case #2:

- Prevalence of NGT with NAFLD than those without
  - 15% versus 70%, P<0.001
- Newly-diagnosed diabetes was more common in those with NAFLD than those without
  - 75% versus 25%, P<0.001
  - T2DM diagnosed in 14% of an apparently healthy population

## Case #2: Treatment

- Hemoglobin A1c 5.9%
- She was disheartened by a diagnosis of NAFLD
- Not interested in starting Metformin
- Preferred lifestyle changes alone
- 3 months later, A1c 6%

## So, are we treating pre-diabetes?

ORIGINAL RESEARCH

Annals of Internal Medicine

Metformin Prescription for Insured Adults With Prediabetes From 2010 to 2012

A Retrospective Cohort Study

Taneez Moles, MD, MBA, MSHS; Jiman Li, MPH; O. Kenrik Duru, MD, MSHS; Susan Ettner, PhD; Norman Turk, MS; Abigail Kekhafer, MBA, MPH; Sam Ho, MD; and Carol M. Mangione, MD, MSPH

- 17352 working age adults with prediabetes
- 3.7% of patients were prescribed Metformin

## What are the barriers to treatment?

- Using Metformin to treat pre-diabetes is off-label
- Patient's hesitance to take medication
- Lifestyle interventions may be superior

## Where do we go from here?

- Identifying those patients who may most benefit
- Informed discussions with patients
- Additional clinical trials



## Who am I treating?

- Informed discussion with your patient is key
- I screen those at high risk based on ADA
  - Awaiting formal USPSTF update
- I have discussions with patients with *all* patients identified as pre-diabetic, especially those who fit the ADA-suggested profile
  - <60 years old
  - Obesity
  - Gestational diabetes

## Who am I treating?

- More inclined to treat patients at high risk for cardiovascular disease and those who cannot achieve high-intensity lifestyle changes
- Discuss Mediterranean Diet