

Prediabetes: To Treat or Not To Treat?

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Disclosures

Dr. Mennen has no financial interest of any kind with products or services discussed during this presentation.

Objectives

1

Define prediabetes, its diagnostic metrics and treatment options

2

Increase familiarity with the risk factors for prediabetes that call for screening

3

Once prediabetes is diagnosed, one or more appropriate interventions with the patient is accomplished by the clinician

Prediabetes is not a disease *per se*

“Prediabetes’ is the term used for individuals with IFG and/or IGT and/or A1C 5.7–6.4%. Prediabetes should not be viewed as a clinical entity in its own right but rather as an increased risk for diabetes and cardiovascular disease (CVD).

“Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.”

The Inevitable Statistics

29 million US adults have T2D or 11.7%

- **255,695 WV adults or 15.3% with T2D (#1 in US)**

82 million US adults have prediabetes or 33.3%

- **518,000 in WV or 35.9% of adult population with prediabetes**

89.7 million US adults are obese (BMI >30) or 36.5%

- **539,000 WV adults or 37.7% are obese (#1 in US, MS #2 @ 37.3%; CO at 22.3% is least obese)**

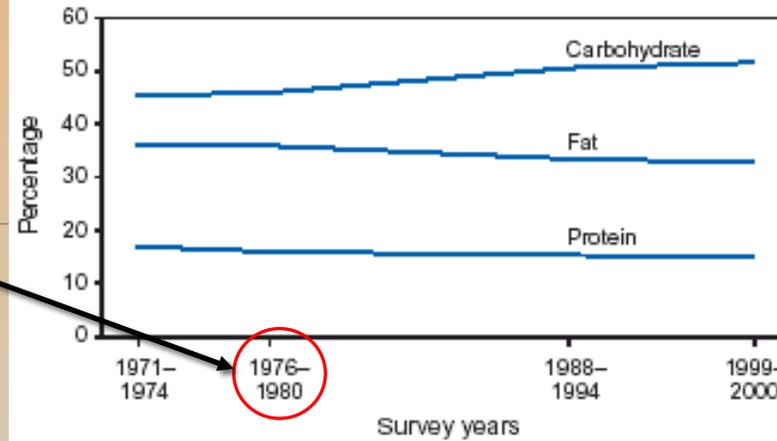
81.4 million US adults are overweight or 33.1%

- **500,500 WV adults or 35% are overweight**

US adult population ≈ 246 mil; WV ≈ 1.8 mil

When we increased
carbs and decreased
fat...

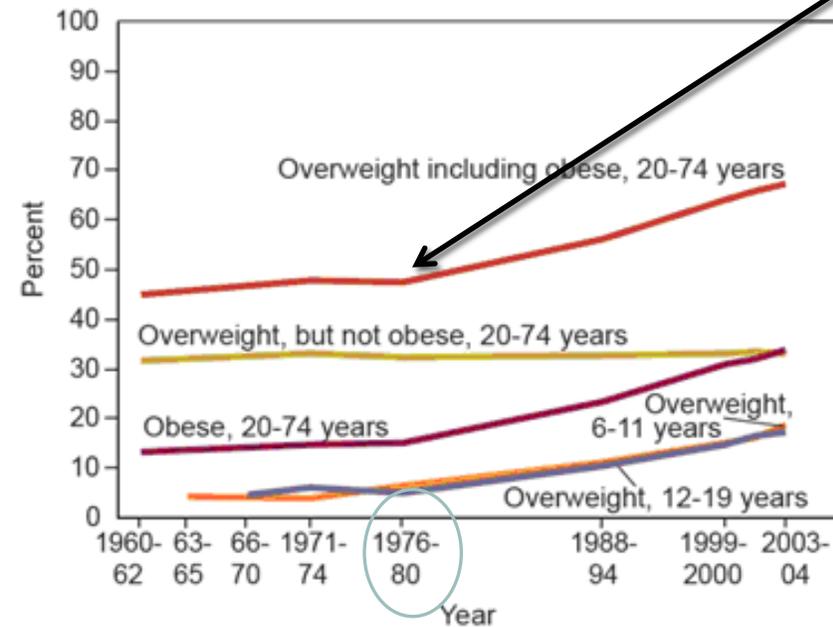
FIGURE 2. Percentage of kilocalories from macronutrient intake among women aged 20–74 years*, by survey years — National Health and Nutrition Examination Surveys (NHANES), United States, 1971–2000



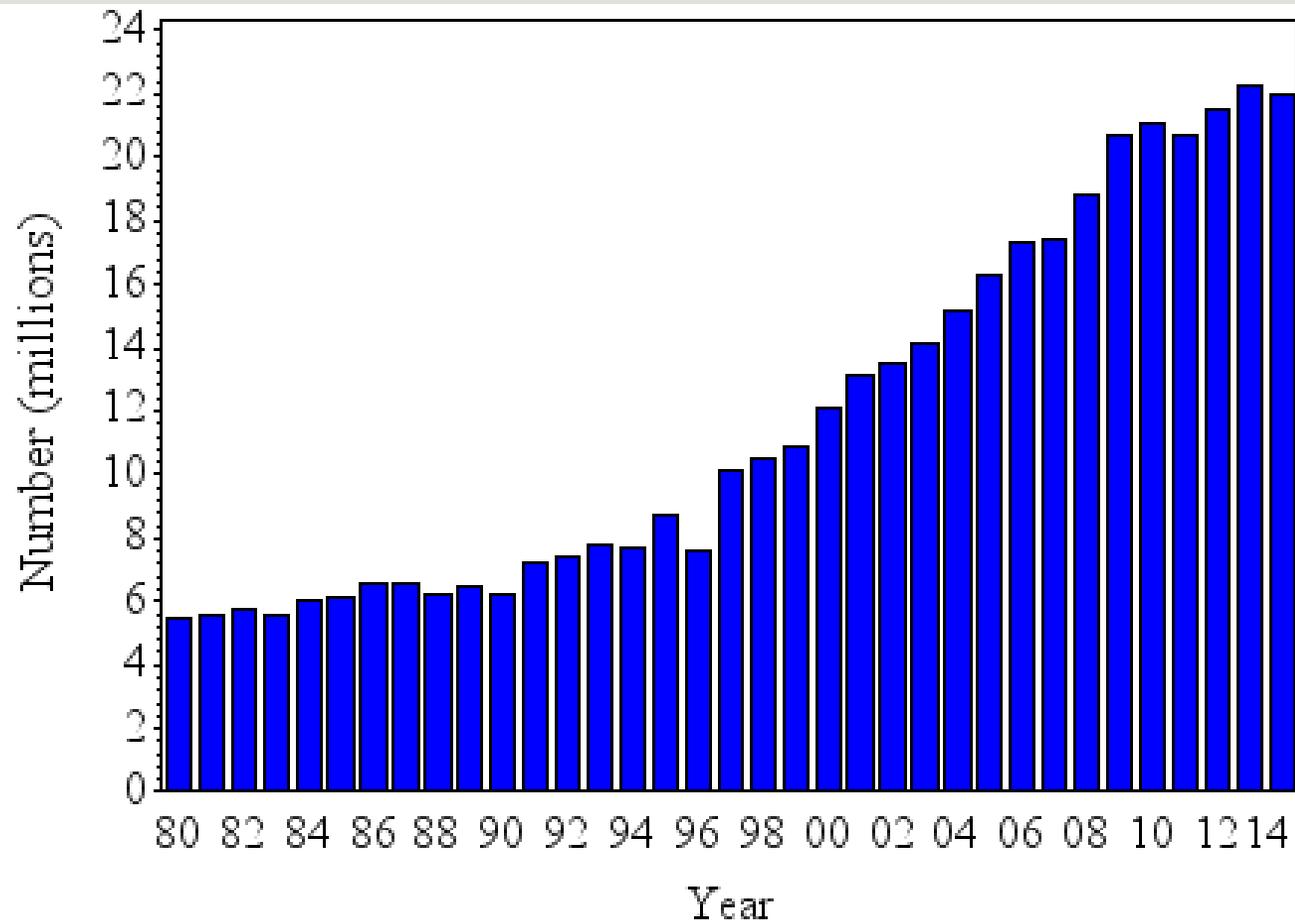
*Age adjusted by direct standardization to the 2000 U.S. Census population by using age groups 20–39, 40–59, and 60–74 years.

Look what began to
happen...

Overweight and obesity

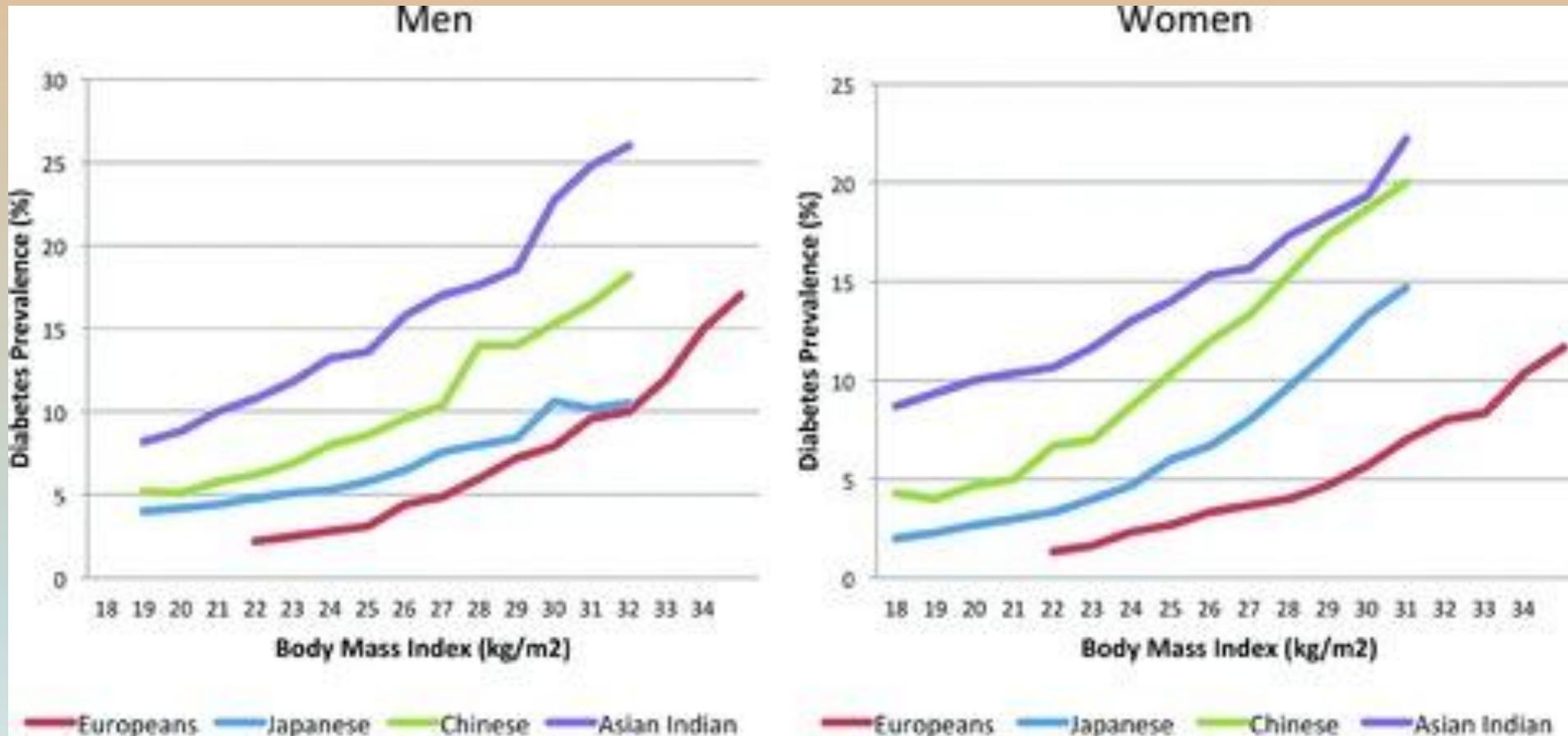


SOURCES: Centers for Disease Control and Prevention, National Center for Health Statistics, Health, United States, 2006, Figure 13. Data from the National Health and Nutrition Examination Survey.

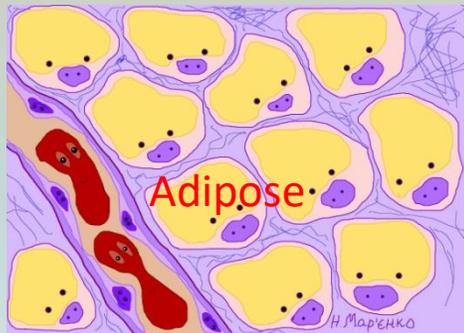
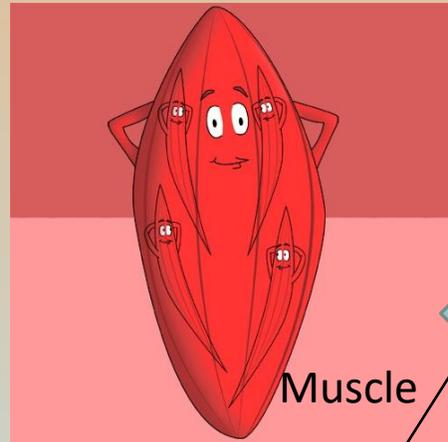


Number of
Persons with
T2D

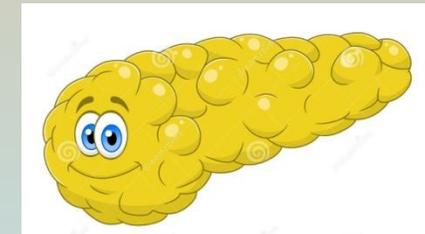
Relationship Between BMI and T2D



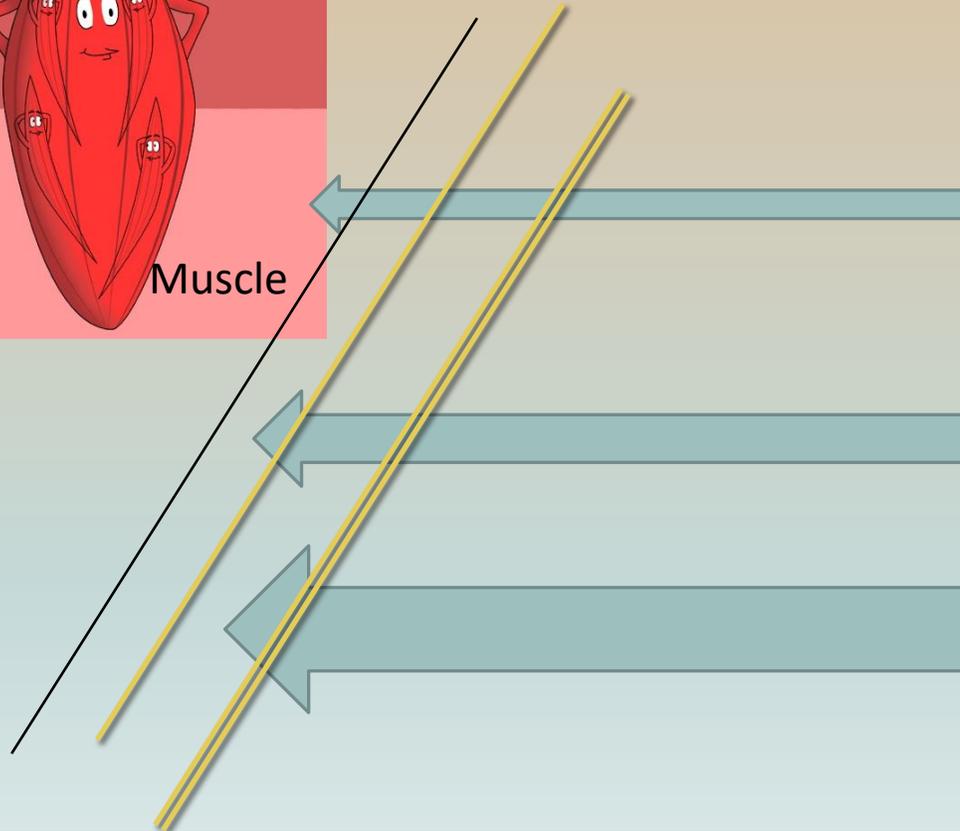
How T2DM Develops



The inability of the pancreas to keep up with the \uparrow demand secondary to \uparrow insulin resistance in the main target tissues is the ultimate cause of prediabetes and diabetes.



Pancreas



T2DM is primarily a disease of
progressive beta cell failure

WHY is T2D, PreD and GD *SO* Common?

Genotypes and Phenotypes

1962

- In 1962, the late James Neel proposed the “thrifty genotype” to explain the high incidence of T2D
 - Neel proposed that during our paleo past with its ‘feast or famine’ existence a more diabetic-like metabolism would be more efficient at storing calories
 - Too many issues have arisen that even Neel (in 1999) dropped the hypothesis

1992

- In 1992, Barker proposed the “thrifty phenotype”
 - hypothesizes maternal undernourishment “programs” the fetus in utero for anti-starvation mechanisms including greater fat storage
 - One adjustment was increased insulin resistance

Who Should Be Screened?

Recommendations: Prediabetes

Screening for prediabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. **B**

Testing should begin at age 45 for all people. **B**

Consider testing for prediabetes in asymptomatic adults of any age w/ BMI ≥ 25 kg/m² or ≥ 23 kg/m² (in Asian Americans) who have 1 or more add'l risk factors for diabetes. **B**

If tests are normal, repeat at a minimum of 3-year intervals. **C**



Recommendations: Prediabetes (2)

FPG, 2-h PG after 75-g OGTT, and A1C, are equally appropriate for prediabetes testing. **B**

In patients with prediabetes, identify and, if appropriate, treat other CVD risk factors. **B**

Consider prediabetes testing in overweight/obese children and adolescents with 2 or more add'l diabetes risk factors. **E**



Prediabetes*

**FPG 100–125 mg/dL
(5.6–6.9 mmol/L): IFG**

OR

2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L): IGT

OR

A1C 5.7–6.4%

* For all three tests, risk is continuous, extending below the lower limit of a range and becoming disproportionately greater at higher ends of the range.

Recommendations: Testing for Type 2 Diabetes

Screening for type 2 diabetes with an informal assessment of risk factors or validated tools should be considered in asymptomatic adults. **B**

Consider testing in asymptomatic adults of any age with BMI ≥ 25 kg/m² or ≥ 23 kg/m² in Asian Americans who have 1 or more add'l dm risk factors. **B**

For all patients, testing should begin at age 45 years. **B**

If tests are normal, repeat testing carried out at a minimum of 3-year intervals is reasonable. **C**



Recommendations: Screening for Type 2 Diabetes (2)

FPG, 2-h PG after 75-g OGTT, and the A1C are equally appropriate. **B**

In patients with diabetes, identify and, if appropriate, treat other CVD risk factors. **B**

Consider testing for T2DM in overweight/obese children and adolescents with 2 or more add'l diabetes risk factors. **E**



Risk factors for Prediabetes and T2D

- A1C \geq 5.7% (39 mmol/mol), IGT, or IFG on previous testing
- first-degree relative with diabetes
- high-risk race/ethnicity (e.g., African American, Hispanic/Latino, Native American, Pacific Islander)
- women who were diagnosed with GDM
- history of CVD
- hypertension (\geq 140/90 mmHg or on therapy)
- HDL cholesterol level $<$ 35 mg/dL (0.90 mmol/L)
- women with polycystic ovary syndrome
- physical inactivity
- other clinical conditions associated with insulin resistance (e.g., acromegaly, Cushing's disease, Cushing's syndrome, hyperthyroidism, hypothyroidism, pheochromocytoma, paraganglioma, and prolactinoma).

American Association of Clinical Endocrinologists
(AACE)

Add:

- Antipsychotic therapy for schizophrenia or bipolar
- Long-term glucocorticoid exposure
- Sleep disorders in the presence of glucose intolerance
- **Overweight (BMI 25-30) or obese (BMI \geq 30)**
- GDM or \geq 9 lb newborn delivered

www.diabetes.org/are-you-at-risk



Criteria for Testing for T2DM in Children & Adolescents

Overweight plus any 2 :

- Family history of type 2 diabetes in 1st or 2nd degree relative
- Race/ethnicity
- Signs of insulin resistance or conditions associated with insulin resistance
- Maternal history of diabetes or GDM

Age of initiation 10 years or at onset of puberty

Frequency: every 3 years

Test with FPG, OGTT, or A1C



Comparison of Diagnostic Criteria for Prediabetes: WHO, AACE, ADA

	WHO (2006)	AACE (2015)	ADA (2017)
IFG	110 mg/dL to 140 mg/dL	100-125 mg/dL	100-125 mg/dL
IGT	FPG < 126 mg/dL and 2h PP 140-200 mgdL	2h PP 140-199 mg/dL	2h PP 140-199 mg/dL
HbA1 _c	Do not use	5.5-6.4%	5.7-6.4%

1) Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia : report of a WHO/IDF consultation. 2006

2) Handelsman, Y et. al. AACE and ACE-Clinical Practice Guidelines for developing a DM comprehensive care plan. Endocrine Practice. 2015 (suppl 1):1-87

3) American Diabetes Association Standards of Medical Care in Diabetes. Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

The Risks of Prediabetes

Diabetes itself is, of course, one risk

- Conversion rate depends on definition of prediabetes, i.e., IFG, IGT or HbA_{1c}
 - The following are annual conversion rates (ranges have generally held true in multiple studies done after Gerstein, et al):
 - Isolated IGT, 4-6%
 - Isolated IFG, 6-9%
 - IGT + IFG, 15-19%
 - HbA_{1c} @ 5.7-6.4%, 7%

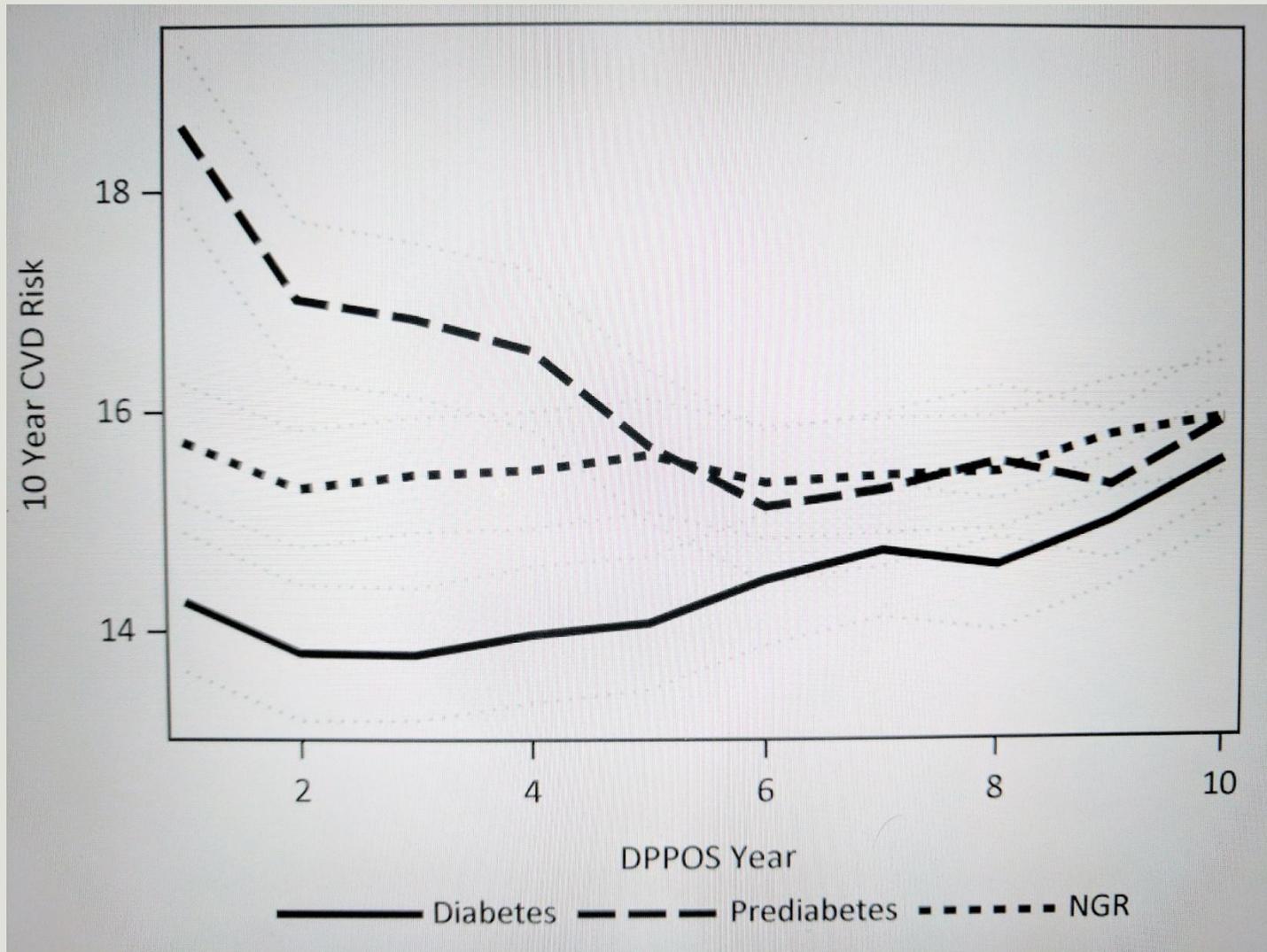
Microvascular disease risk

- An association between prediabetes and nephropathy had been reported, but the latest data do not support those findings¹
- Prediabetes carries the same risk for peripheral neuropathy as newly diagnosed T2D² i.e., 50% when screened.
- In patients with prediabetes, a large study (1,100 with prediabetes) found the incidences of diabetic retinopathy at 8.1% and maculopathy at 0.2% Most of the DR was mild³

- 1) [Xing FY, et al. Diab Vasc Dis Res.](#) 2014 Jan;11(1):11-8
- 2) Lee, CC, et al. [Diabetes Care.](#) 2015 May;38(5):793-800
- 3) Lamparter J, et al. [J Diabetes Complications.](#) 2014 Jul-Aug;28(4):482-7

Macrovascular complications

- Because there usually are a number of other variables present in prediabetes that are independent risk factors for CV disease (e.g., obesity, HTN, dyslipidemia) it is often difficult to tease out a separate role for prediabetes
- However, data from the DPPOS show that the CV risk in the prediabetic state can be ameliorated by reversion to normoglycemia, whereas history has shown that better glucose control in T2D does not affect CV morbidity and mortality



Treating Prediabetes

OR NOT?

Lifestyle Changes

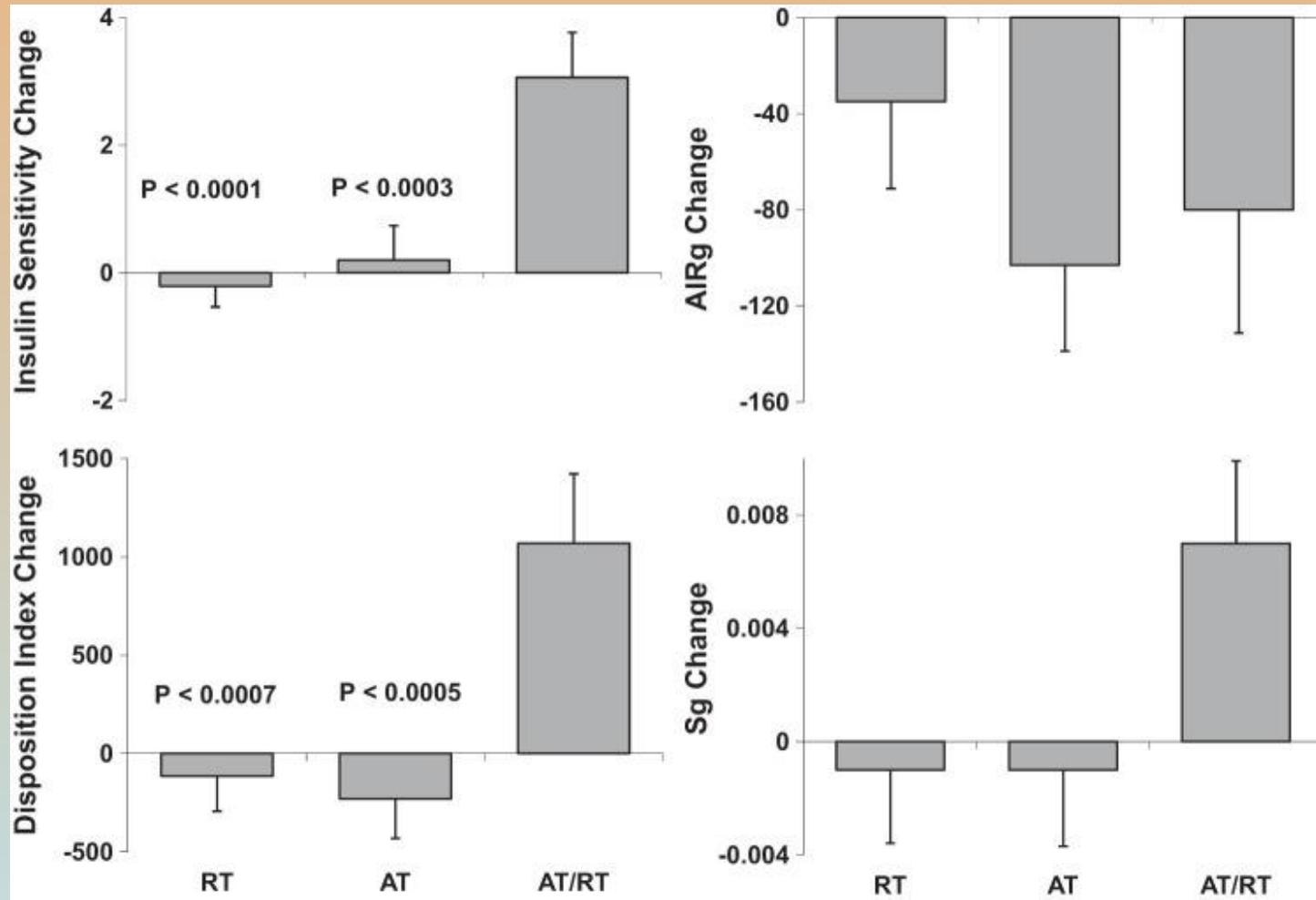
- Weight loss
 - Losing weight in the short term is easy, maintaining the loss is hard
 - Programmed diets (Weight Watchers, Nutrasystem) have very high failure rates
 - YOU have to make the weight loss a matter of life or death (without scaring the patient, of course)
 - For every 1 kg decrease in weight, a 16% risk reduction for developing T2D was achieved*
- Dietary change
 - [My opinion] Initially sending them to a dietitian sends the wrong message (“It’s not really important enough for me to talk about it with you”)
 - Lifestyle NOT diet
 - “Look, you’ve had your fun, but we need to make some changes to save your life.”
 - “Many people can avoid drugs or keep them to a minimum if they get serious about carbs.”
 - “This does not mean you’ll never have a pizza or ice cream again, but let’s get you started before we start talking about that.”

*Knowler WC, et al DPPRG. *N Eng J Med* 2002;**346**:393-403

Lifestyle change (2)

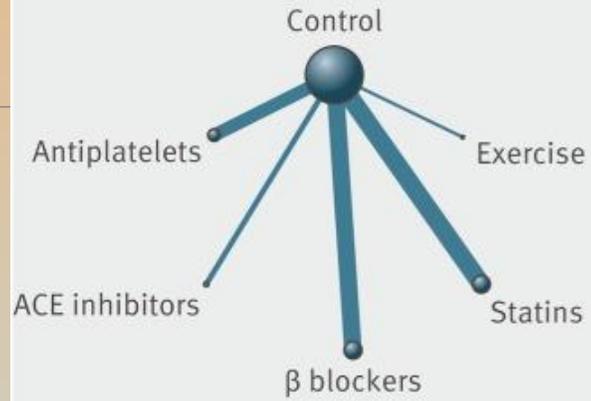
- Exercise
 - Aerobic activity and resistance training do different things
 - Resistance training (free weights, machines, graded bands, resistance exercise) lower insulin resistance in the skeletal muscle
 - The various components of lifestyle change (weight loss, diet and exercise) and usually not teased apart when the “lifestyle” effect reported.

Aerobic Plus Resistance

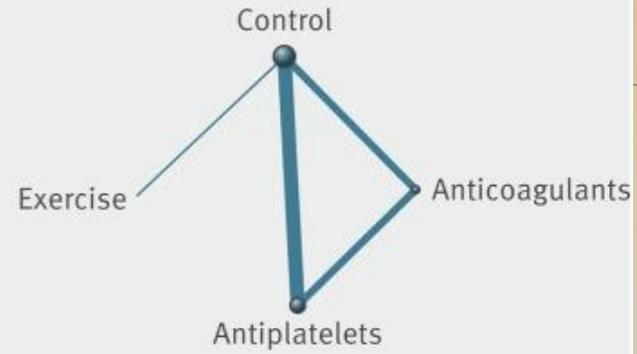


AbouAssi H, et al J Appl Physiol (1985). 2015 Jun 15; 118(12): 1474–1482

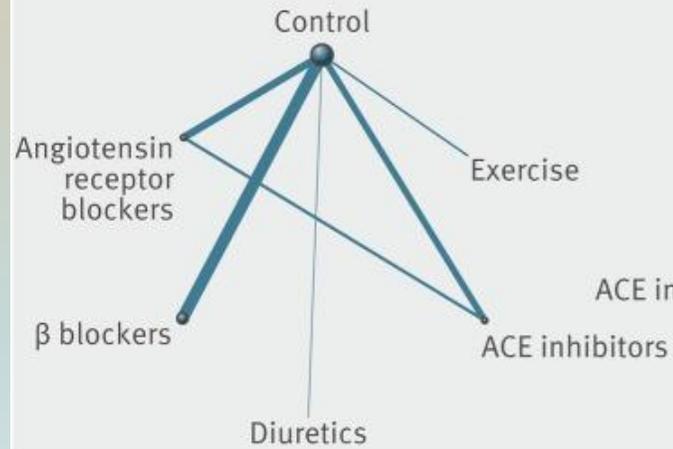
Coronary heart disease



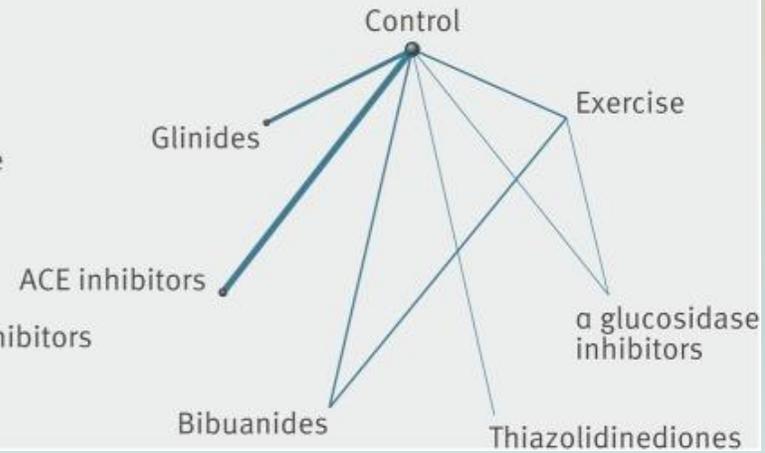
Stroke



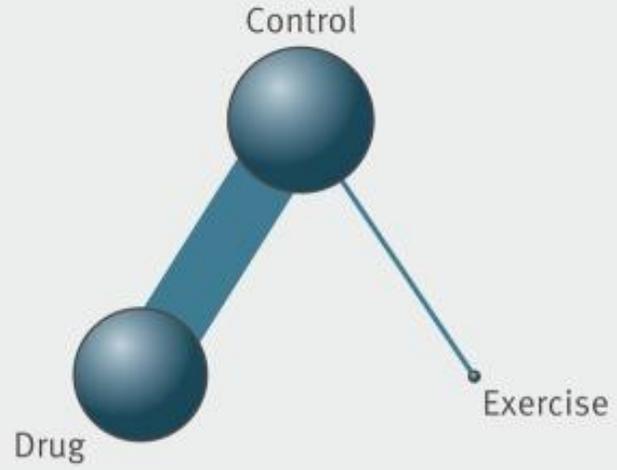
Heart failure



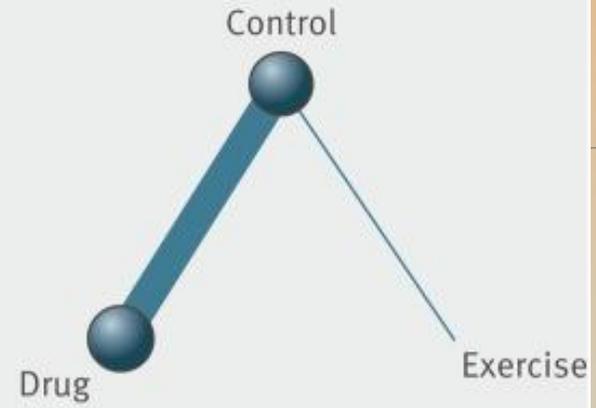
Prediabetes



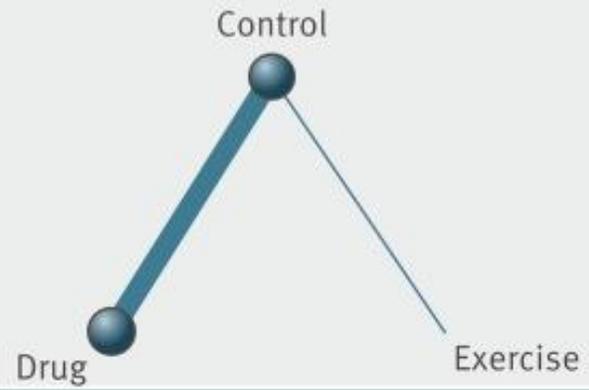
Coronary heart disease



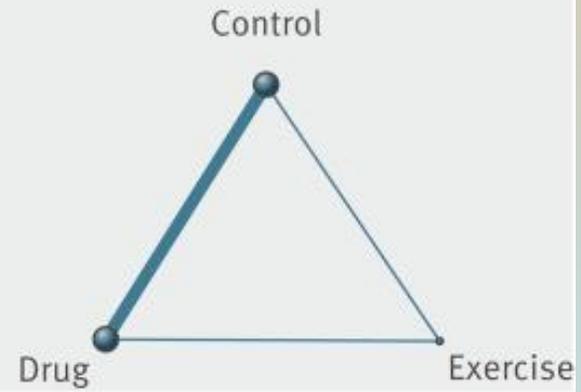
Stroke



Heart failure



Prediabetes



Medications to treat prediabetes

Metformin

- Collective evidence suggests 45% reduction in risk for T2D
 - In the US DPP trial, MET was less effective than lifestyle, but in other trials equal to or better than
 - Lowers hepatic insulin resistance (↓ gluconeogenesis)
 - Now being studied for longevity and anti-cancer effects
 - Can lead to B12 insufficiency
 - Abdominal pain and diarrhea frequent at start of Tx—(avoid by Rx 500 mg ½ tab q am x 1 wk, then ½ tab bid x 1 more wk, then 1 tab bid)
 - Do not initiate MET if eGFR <45
 - Helps patients lose weight, but more beneficial to pts with higher BMIs

Acarbose

- Acarbose blocks the enzymatic breakdown of starches and disacharrides
- Hmmm...blocks the absorption of carbs...what if we recommended lower carb diets? (The [American Diabetes Association](#) has recommended that 60–70% of caloric intake should be in the form of [carbohydrates](#) until a few years ago)
- In the STOP-NIDDM trial* acarbose ↓ the risk of T2D developing by 25% in 3.3 years
 - 31% dropped out (flatulence, diarrhea)

Glitazones

- Rosiglitazone showed 60% decrease in risk for T2d over 3 years
- Weight gain, ↑CHF CV events
- Pioglitazone ↓ risk by 70%
- Very effective, but side effects knock them out

Others

GLP-1 analogs

DPP-4 inhibitors

Bariatric Surgery

To come

Summary

- As clinicians, we “let the punishment fit the crime,” i.e., we match the aggressiveness of therapy with the seriousness of the condition
- Dietary and exercise upgrades are the mainstays of therapy and should always be encouraged by the physician
- Metformin therapy (IMO) should be started in obese patients with evidence of significant insulin resistance (IR)
 - A reasonable approximation of IR can be done by inserting fasting blood glucose with concomitant insulin level into a formula, the HOMA-IR. This can be helpful in differentiating between patients with mainly IR or secretion issues
- We should certainly be intervening with more patients with prediabetes than we currently are
- Although success is seen with the prevention of T2D using lifestyle and/or drug therapy, benefits difficult to show for complications other than stroke risk and retinopathy,
- The risks with HbA_{1c} between 5.5 and 5.9% are significantly less than 6.0 and 6.4%, so, IMO, a different approach should be taken at these intervals
- Also: Patient’s age? BMI? Family Hx? Motivation? Like with all else, we must individualize approach
-
-

Thank you!

Gestational Diabetes(GD)

GD incidence 9.2% in US

In whites, it is 3.3%, while in Pakistani Americans it is 15%