A GLYCEMIC JOURNEY

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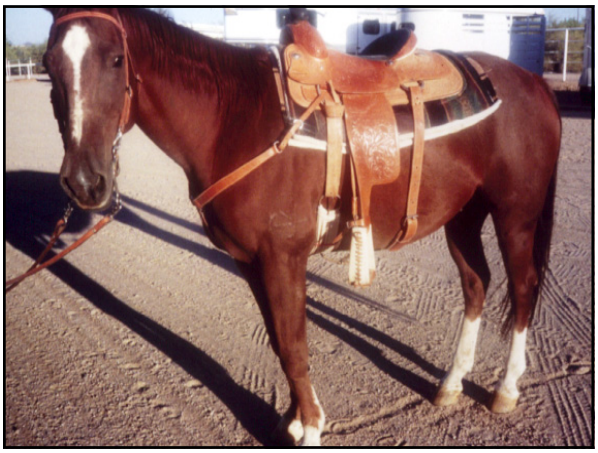
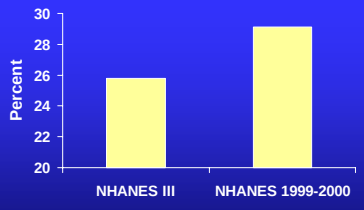


OBJECTIVES

- Understand progressive nature of glucose intolerance in persons at risk for diabetes
- Understand how glucose intolerance phases are defined
- Know how to approach management of the different phases of glucose intolerance

The Evolution of Man

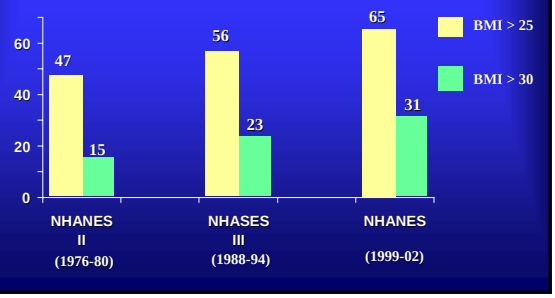
METABOLIC SYNDROME IN THE U.S. PREVALENCE CHANGES



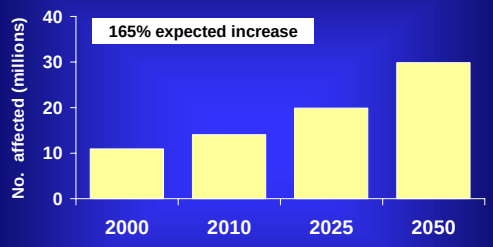
From: Ford et.al., Diabetes Care 27:2444,2004

AGE ADJUSTED PREVALENCE OF OVERWEIGHT/OBESE IN THE U.S.

ADULTS > 20 yrs.



PROJECTED U.S. DIABETES PREVALENCE



Diabetes is now and will continue to be an important and high profile public health issue

From: Boyle et.al., Diabetes Care 24:1936,2001

The NEW ENGLAND JOURNAL of MEDICINE
NEJM 2005; 352;1138

SPECIAL REPORT

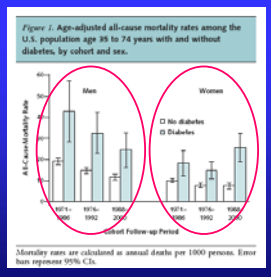
A Potential Decline in Life Expectancy in the United States in the 21st Century

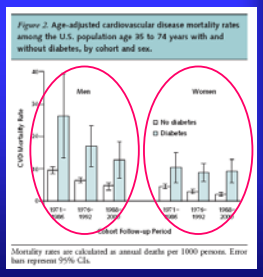
S. Jay Olshansky, Ph.D., Douglas J. Passaro, M.D., Ronald C. Hershow, M.D., Jennifer Layden, M.P.H., Bruce A. Carnes, Ph.D., Jacob Brody, M.D., Leonard Hayflick, Ph.D., Robert N. Butler, M.D., David B. Allison, Ph.D., and David S. Ludwig, M.D., Ph.D.

"…we conclude that the steady rise in life expectancy during the past two centuries may soon come to an end."

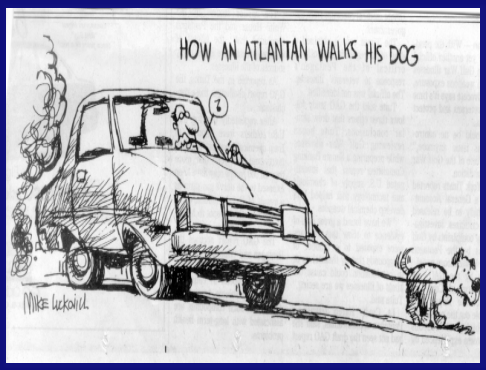
"This reduction in life expectancy is not trivial— it is larger than the negative effect of all accidental deaths combined .... and there is reason to believe that it will rapidly approach and could exceed the negative effect that ischemic heart disease or cancer has on life expectancy."

GENDER DISPARITIES IN MORTALITY





Annals of Internal Medicine 2007 147:149-155



GLUCOSE TOLERANCE CATEGORIES

Category	Fasting glucose (mg/dl)	2 hr glucose (mg/dl)
Normal	70 to 100	<140
Impaired Fasting Glucose (IFG)	101 to 125	<140
Impaired Glucose Tolerance (IGT	70 to 100	140 to 199
Diabetes	≥126	≥200

ADA DIAGNOSTIC CRITERIA

Symptoms plus casual glucose ≥200mg/dl

or

FPG ≥126mg/dl*

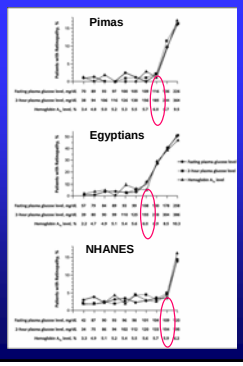
or

2-h glucose ≥200 mg/dl during 75 gm OGTT*

***Must have confirmatory test on separate day**

Where Does The Fasting Criteria For Diabetes Diagnosis Come From?

- Fasting glucose cut-off based on analysis of three populations
- Threshold for diagnosis is point where risk of retinopathy increased



Ann Intern Med 2002;137:263-272

A1C AND DIAGNOSIS OF DIABETES

- Advantages
  - Easy and convenient
  - +2 SD above nondiabetic mean has similar sensitivity and specificity to FPG
- Disadvantages
  - Lack of standardization
  - Affected by other processes
    - Transfusion
    - Hemolysis

Natural History Of Glucose Intolerance And Corresponding Interventions

Normal Glc. Tolerance	Impaired: Fasting Glc Glc. Tolerance	Diabetes mellitus		
Assess Risk	Prevention strategies	Lifestyle	Orals	Insulin

We will use hypothetical case to trace one person's journey through different phases of glucose tolerance

Adapted from Diabetes Care, 27:S5, 2004

SCENARIO

- A 32 year old Hispanic woman comes for her physical
  - Works in housekeeping, runs around all day, BMI = 26 kg/m2, fasting glucose is 82 mg/dl
  - 3 children under 10
  - She asks: "Doc, my grandpa, mom and older brother have diabetes. What are my chances of getting it, too?"

What do you tell her?

Natural History Of Glucose Intolerance And Corresponding Interventions

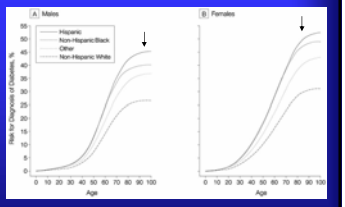
Normal Glc. Tolerance	Impaired: Fasting Glc Glc. Tolerance	Diabetes mellitus		
Assess Risk	Prevention strategies	Lifestyle	Orals	Insulin

Where is our patient now?

Adapted from Diabetes Care, 27:S5, 2004

LIFETIME RISK OF DEVELOPING DIABETES

- Estimate of life time risk of diabetes in cohort born in 2000 from birth to 80 years
- 33% for women
  - 11.6 years life lost
- 39% for men
  - 14.3 years life lost
- Highest life time risk among Hispanics
  - 45% for men
  - 53% for women



JAMA 2003;290:1884-1890

WHO TO SCREEN

- Screen at 3 year intervals in persons:
  - Beginning at 45 years of age
  - BMI ≥25 kg/m^2
- Screen earlier or more often in people with high risk demographic features:

HTN	GDM or baby >9lbs
Dyslipidemia	History of IFG, IGT
Family history	PCOS
Sedentary	Vascular disease
Race/ethnicity	

Diabetes Care, 27:S5, 2004

HOW TO SCREEN

- Fasting plasma glucose (FPG) preferred
  - Faster
  - Easier
  - More convenient
  - Cheaper
  - Greater patient acceptance
- Consider OGTT in persons in whom suspicion is high and FPG is not normal

Diabetes Care, 27:S5, 2004

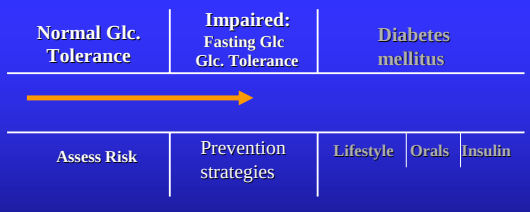
Back to our patient…
So, what can you tell her ?

- Does she have diabetes?
- She is at high risk for developing diabetes
- I would screen her yearly
- Provide diet and exercise counseling

Follow up:

- You see the same patient 3 years later; BMI is now 28 kg/m^2
- A fasting glucose is 116 mg/dl
- You decide to do a 2h OGTT: her 2h value is 179 mg/dl

Natural History Of Glucose Intolerance And Corresponding Interventions



Where is our patient now?

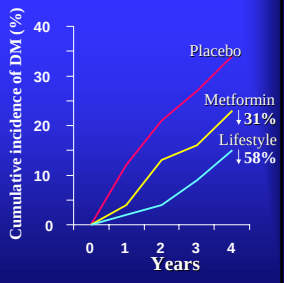
SO NOW WHAT ?

- How is her fasting glucose classified?
  - Impaired fasting glucose (IFG)
- How is her 2h glucose classified?
  - Impaired glucose tolerance (IGT)
- Has her glucose tolerance deteriorated?
  - Yes
- What designation do we give someone with IFG or IGT?
  - Prediabetes

CAN WE PREVENT PROGRESSION TO DIABETES?

DIABETES PREVENTION PROGRAM

- DPP
  - > 25 yrs. of age
  - BMI > 24
  - FPG 95-125
  - 2 h glc. 140-199
- Randomized to:
  - Placebo
  - Metformin
  - Lifestyle change (150 min/wk exercise + 7% reduction in weight)



NEJM 346:393, 2002

OTHER DIABETES PREVENTION TRIALS

- Da Qing IGT and Diabetes Study
  - Control vs. Diet vs. Exercise vs. Diet + Exercise
  - 40% reduction in diabetes
- Finnish Diabetes Prevention Study
  - Lifestyle vs. control
  - 60% reduction
- DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication)
  - 8mg Rosiglitazone vs control
  - 60% reduction

Diab Care 20:537, 1997: NEJM 344:1343, 2001; Diab Care 31:1007, 2008

What do you tell your patient now?

- She has pre-diabetes
- She can most effectively delay or prevent his diabetes by:
  - Eating right
  - Exercising
  - Losing weight

"I'll try, doc"

What are the odds of her implementing a DPP type program in her life?

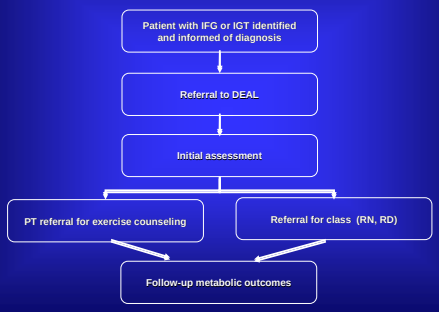
How can a DPP type approach be translated to a real-world setting?

DEAL

Diet - Education - Activity - Lifestyle

"Promoting Healthy Lifestyles"

Organization of DEAL Program



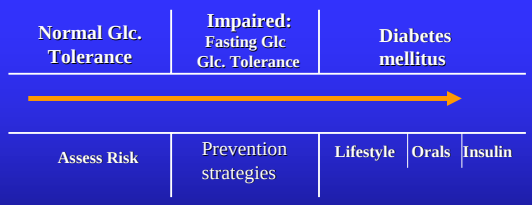
DEAL algorithm

Back to the patient:

- Your patient is now 42 years old
- She hasn't been back for nearly 6 years
- "I've been busy, doc. College for the kids is coming up around the bend. I work two jobs now"
- Lately has been feeling fatigued, complaining of some numbness in her feet—"My mama felt that way when she got diabetes"
- Random glucose is 257 mg/dl, A1c 8.5%

What do you do now?

Natural History Of Glucose Intolerance And Corresponding Interventions



Assess Risk	Prevention strategies	Lifestyle	Orals	Insulin

Where is our patient now?

Adapted from Diabetes Care, 27:S5, 2004

Update on Therapeutic Strategies in Type 2 Diabetes

Objectives

- Continue with our scenario from prior talk
- Therapeutic strategies in Type 2 diabetes

This is not going to be "drug talk"!

More about reviewing current opinions and controversies about strategies of care in type 2 diabetes

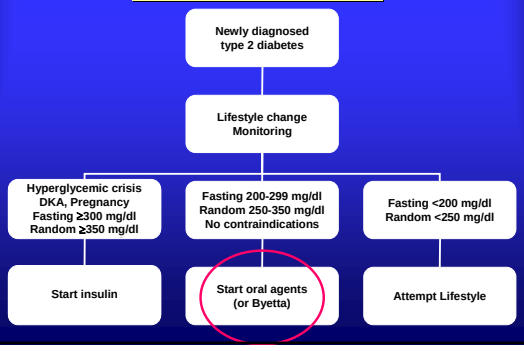
Rx APPROACH IN NEWLY DIAGNOSED DIABETES

NON-PHARMACOLOGIC

- Refer for education
- Start SMBG
- Check Eyes
- Assess other CVD risk factors
  - BP
  - Lipids
  - Urine microalbumin
  - ECG
  - ASA a day

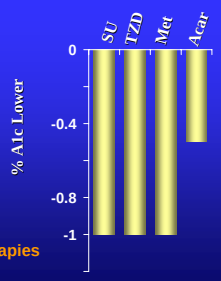
Rx APPROACH IN NEWLY DIAGNOSED DIABETES

DRUG INTRODUCTION



ORAL AGENTS AND A1c LOWERING

- All monotherapies decreased HbA1c by 0.5-1%
- Metformin had greatest benefit on weight and LDL lowering
- SU had most hypoglycemia

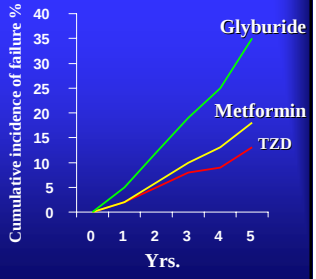


Moral: all non-insulin monotherapies are created equal

Ann Intern Med 2007;147:386

Glycemic Durability A Diabetes Outcome Progression Trial (ADOPT)

- Failures at 5 years
  - Glyburide: 34%
  - Metformin: 21%
  - Rosiglitazone: 15%



NEJM 2006;355:2427

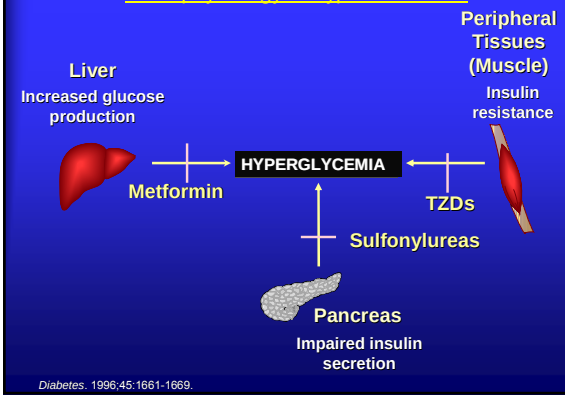
Dose-Response-Adverse Effects Relationship

- Most drugs exert maximum benefit at submaximal doses
- Attempting to maximize dose leads to more side effects without improving therapeutic result

Argues for earlier introduction of combination therapies that augment each other

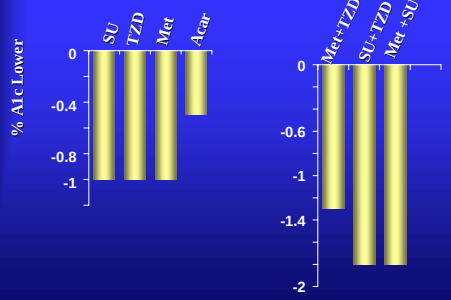
Diabetes Care 2008 31 (2):S125

Pathophysiology of Type 2 Diabetes



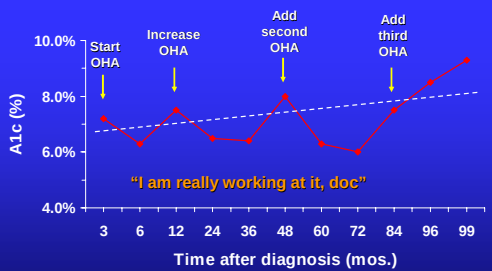
Diabetes. 1996;45:1661-1669.

ORAL AGENTS AND A1c LOWERING



Ann Intern Med 2007;147:386

How does your patient do?

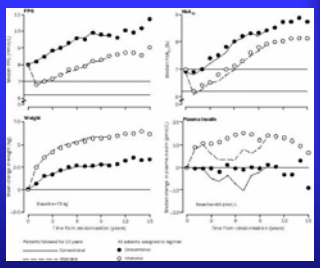


Why is her control deteriorating?

So now what???

DIABETES TENDS TO GET WORSE

- Progressive loss of glycemic control
- Insulin secretion declines
- More complex therapies required



It's not the patient's fault!!

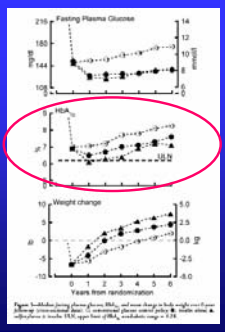
UKPDS--Lancet 352:854, 1998

INSULIN Rx SOONER RATHER THAN LATER

- Pros
  - Improved glucose disposal
  - Suppresses hepatic glucose output
  - Improves β-cell function/survival
  - Can achieve effective glucose control
- Cons
  - Weight gain
  - Hypoglycemia
  - Patient reluctance

INSULIN Rx SOONER RATHER THAN LATER

- UKPDS subanalysis
- Added insulin to people who failed sulfonylurea Rx
- Followed over 6 years
- Found better reduction of A1c when insulin was added earlier

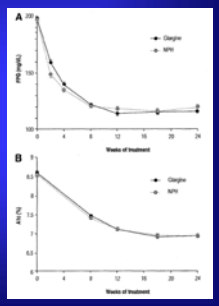


Diabetes Care 2002 25:330

The Treat-to-Target Trial

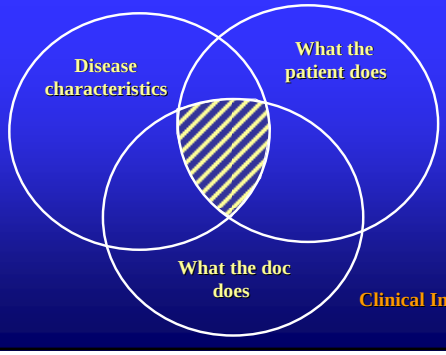
Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

- Looked at patients who failed single or dual oral agent therapy
- Added NPH or Glargine at bedtime
- Comparable improvements in glycemic control
- Glargine associated with fewer hypoglycemic episodes



Diabetes Care 2003 26:3080

WHAT DETERMINES Rx SUCCESS?



STEP WISE APPROACH TO DM Rx

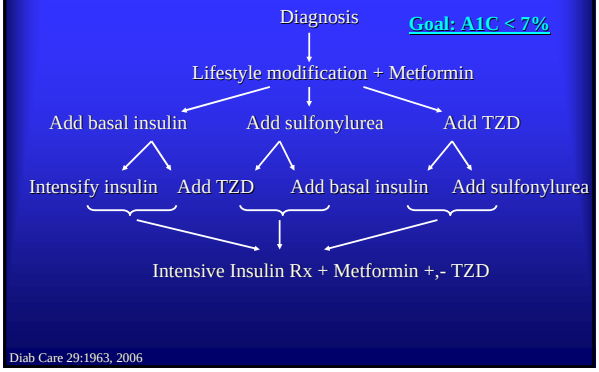
Expect to have to intensify therapy over time

Avoid clinical inertia

Make significant changes

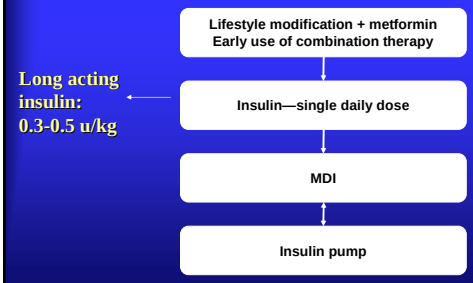
- Lifestyle modification
- Monotherapy
- Combination (non-insulin) therapies
- Insulin (Once or twice daily ±combinations)
- MDI (±combinations)
- Insulin pump (±combinations)

TYPE 2 DM Rx ALGORITHM
(ADA, EASD-2006)



Diab Care 29:1963, 2006

MODIFIED STEP APPROACH TO DM Rx



DECISIONS, DECISIONS, DECISIONS

- Severity of hyperglycemia
- How far are they from goal?
- How long have they had diabetes?
- Cost
- Contraindications
- Patient desire

CONCLUSIONS

- Hyperglycemia is progressive
- Each phase of glucose tolerance is defined based on the glucose level
- Type 2 diabetes can be delayed
- Effective type 2 diabetes treatments are available
  - Consider early use of combination therapy
  - Consider early use of insulin
  - Expect to have to intensify—avoid clinical inertia

Questions?


Generation O

Arizona looks to get your kids slim, healthy

KIDS IN ARIZONA

Of low-income children ages 4 and younger, nearly

31%

WERE REPORTED TO BE OVERWEIGHT LAST YEAR

up from 26.5 percent in 2001.

U.S. COMPARISON

19th

IS ARIZONA'S RANK

among states in the percentage of obese high school students.

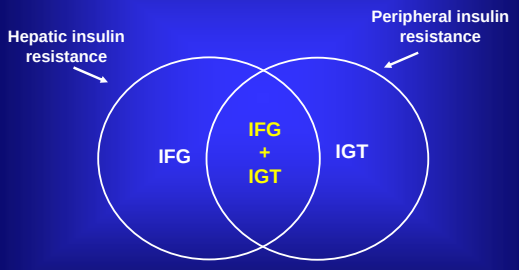
SCHOOLS FALL SHORT

'F'

IS ARIZONA'S GRADE

for its failure to mandate PE, improve nutrition in schools and eliminate junk food on campus, according to the University of Baltimore Obesity Initiative.

The Pre-diabetes Population



Recent examples

- 55 y/o man, 1 week polyuria/polydipsia, glucose 1,067 mg/dl, A1c 10.4%
- 74 y/o man, FPG 136 mg/dl, A1c 6.9%
- 81 y/o woman, 1 year lower extremity numbness, glucose 267 2 h after 75 gm glucose load
- 77 y/o woman, 2 years burning on soles of feet, FPG 201 mg/dl, A1c 7.0%
- 45 y/o man, FPG 105 mg/dl, A1c 6.2%

Risk Assessment

- A study of over 1,000 Egyptians and over 1,000 U.S. residents yielded the following equation
  - $X = -10.0382 + [0.0331$ (age in years) $+ 0.0308$ (random plasma glucose in mg/dl) $+ 0.2500$ (postprandial time assessed as 0 to 8 h) $+ 0.5620$ (if female) $+ 0.0346$ (BMI)$]$
  - If P > 0.20, further testing required

http://www.ndep.nih.gov/ddi/resources/DDI_calc2.htm

Objectives for this Lecture

- Understand scope and basis of problem
- Review definitions of glucose tolerance
- Risk assessment
- Screening for diabetes
- Diabetes prevention strategies

Assessing Personal Risk For Having Diabetes

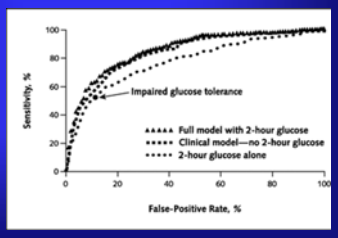
	Yes	No
•My weight is equal to or above that listed in the chart below?	5pts	0pts
•I am under 65 years of age and I get little or no exercise during a usual day?	5pts	0pts
•I am between 45 and 64 years of age?	5pts	0pts
•I am 65 years old or older?	9pts	0pts
•I am a woman who has had a baby weighing more than nine pounds at birth?	1pts	0pts
•I have a sister or brother with diabetes?	1pts	0pts
•I have a parent with diabetes?	1pts	0pts

0 to 9 points: *probably* low risk >10 points: see your doc

From: Herman et.al., Diabetes Care 18:382, 1995

Identification of Persons at High Risk for Type 2 Diabetes Mellitus: Do We Need the Oral Glucose Tolerance Test?

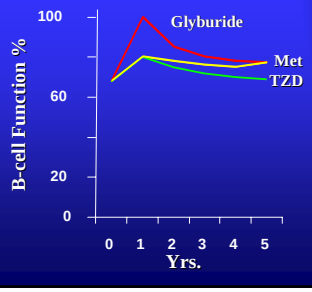
The 2h glucose has less ability to predict future diabetes than a fasting glucose



Stern, M. P. et. al. Ann Intern Med 2002;136:575-581

MAINTAINENCE OF B-CELL FUNCTION (ADOPT)

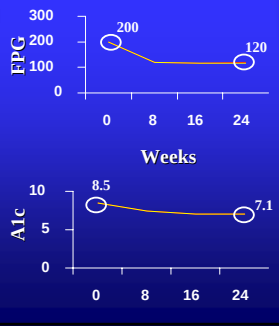
- Worst with glyburide
- Best with rosiglitazone



NEJM 2006;355:2427

TREAT TO TARGET TRIAL INSULIN + ORAL AGENTS

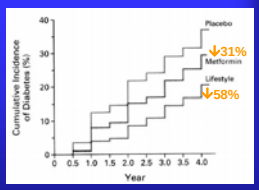
- Looked at patients who failed single or dual oral agent therapy
- Added NPH or Glargine at bedtime
- Comparable improvements in glycemic control
- Glargine associated with fewer hypoglycemic episodes



Diabetes Care 2003 26:3080

Diabetes Prevention Trials

- Diabetes Prevention Program
  - ≥25 years of age
  - BMI ≥24
  - Fasting glucose 95–125
  - 2h glucose 140–199
- Patients randomized to
  - Placebo
  - Lifestyle (150 min/week exercise, goal of 7% loss of body weight)
  - Metformin



Metformin less effective among older patients and those with lower BMI

NEJM 346:393;2002

Other Diabetes Prevention Trials

- Indian Diabetes Prevention Program
  - Like U.S. DPP but had a lifestyle + metformin arm
  - About a 28% reduction in each arm vs. control
  - No added benefit of adding metformin to lifestyle
- Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS)
  - Orlistat vs. placebo
  - 37% decrease

Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes

- Patients who failed oral agent therapy randomly assigned to:
  - Basal insulin (Detemir) only
  - Prandial only (Aspart)
  - Biphasic only (Novolin 70/30)
- Comparable reductions in A1c, although basal alone was not as good
- More hypoglycemia in the prandial alone