

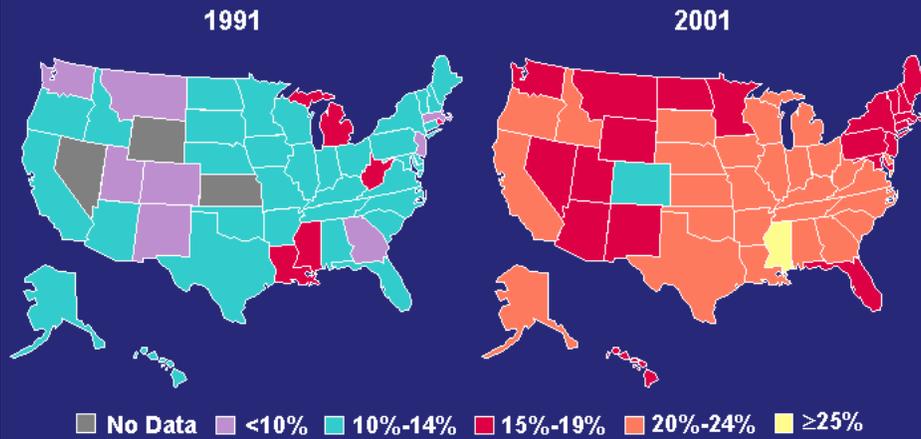
Diabetes Prevention

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Diabetes Prevention: Agenda

- Diabetes: Problem of Epidemic Proportions
- Why are we Gaining Weight?
- What is “Insulin Resistance / Metabolic Syndrome”?
- Cardiovascular Implications of Metabolic Syndrome and Diabetes
- Prevention of Type 2 Diabetes
 - Lifestyle modifications
 - Pharmacologic agents
- Are You at Risk? What can you do to minimize risk of diabetes for yourself and your family?

Prevalence of Obesity* Among US Adults



*BMI ≥ 30 kg/m².

Mokdad AH, et al. JAMA. 2003;289:76-79.
Mokdad AH, et al. JAMA. 1999;282:1519-1522.

State Fair of Texas: Beware the Fried Twinkie



Human History and Obesity

- The human genome was defined 50,000 to 100,000 years ago at a time when the human diet was vastly different than it is today
- Human DNA remodels at a rate of only 0.5% per million years
- The American diet has changed drastically in the last 100 years, with more fat, calories and refined carbohydrates in our foods

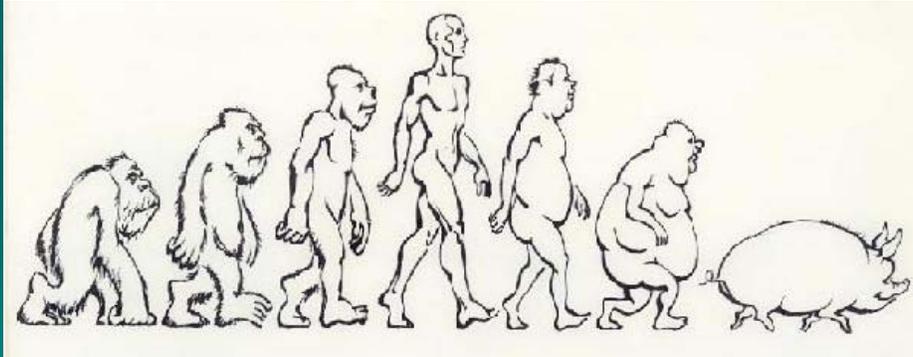
Obesity and the “Thrifty Gene”

- Ancient humans were well adapted to starvation and subsisted on a very high-fiber, low-fat diet
- The ability to hang onto calories efficiently was a survival factor for ancient humans
- The adaptation to starvation is a detriment in our overnourished, underactive society

Well-Adapted to Starvation : Poorly Adapted to Overnutrition

Evolution of Man

1900 2000



Change in Diets from Then to Now

> 50,000 Years Ago

- Fruits, nuts, seeds, roots, tubers, flowers, leaves, stalks, beans
- Low fat with 2-3 x the protein
- No dairy or refined flour
- No processed foods
- No alcohol, tobacco

> Today

- Potato, refined pasta, white rice, corn, refined cereals, white flour
- Added fat and sugar
- High fat proteins
- Ice cream, cheese and whole milk
- Processed foods

Increased Calories

1950
100 kcal



Classic Coke
8 fluid oz

2002
630 kcal



Extreme Gulp
52 fluid oz

280 kcal



"Old Days"
Hamburger

1120 kcal



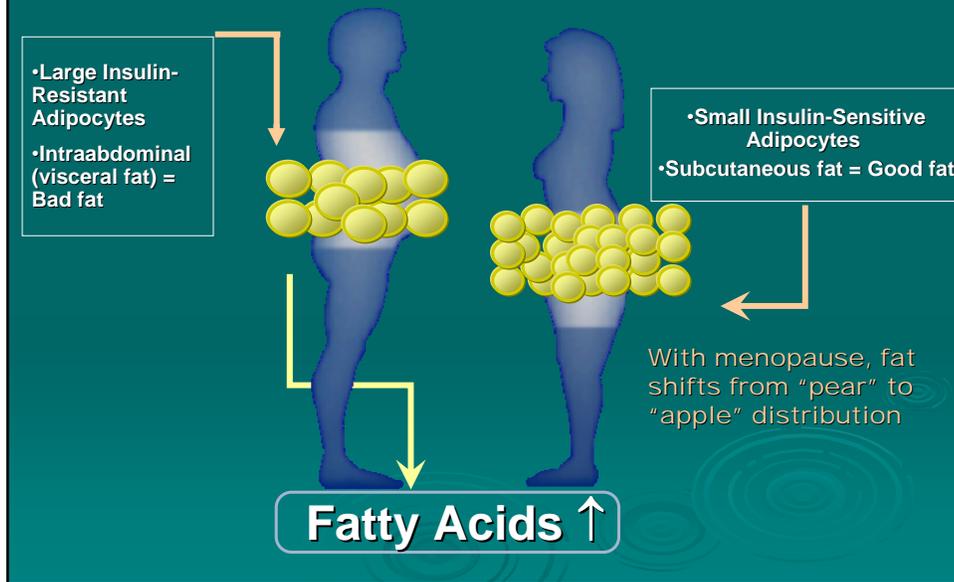
Double Whopper with Cheese

From Active to Sedentary Lifestyle☹

Manually change channel	→ Remote control
Cook for 30 min	→ Pizza delivered
Wash car	→ Go to car wash
Rake leaves for 30 min	→ Leaf blower
Walk dog	→ Let dog out
Unload shopping cart	→ Cashier unloads cart
Shop at mall	→ Shop online
Climb Stairs	→ Escalator



All Fat Cells Are Not Created Equal



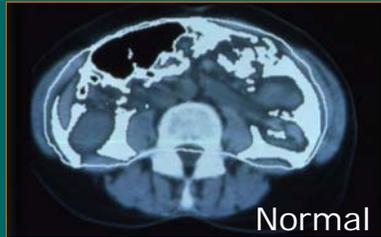
Which is the Evil? Fat or its Location?

Liposuction does not improve metabolic parameters and therefore would not be expected to reduce risk of diabetes or heart disease...



NEJM June 17, 2004; 350:2549-57.

Significance of Abdominal Fat: Visible vs. Visceral



The white “bright” signal on the CT scan represent fat tissue. Fat tissue in the abdomen known as “visceral fat” is the metabolically “bad” fat & sign of insulin resistance.



CT scans Courtesy of Wilfred Y. Fujimoto, MD.



AHA/NHLBI: Updated Metabolic Syndrome Guidelines

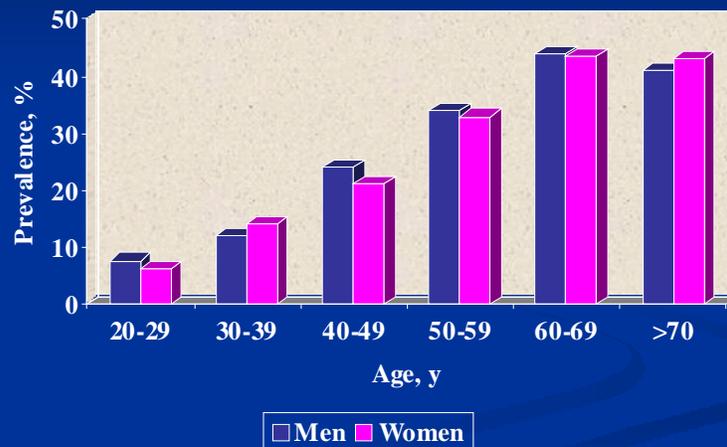
Diagnose when ≥ 3 of these risk factors present

Risk Factor	Defining Level
Waist circumference	
Non-Asian Men*	>40 in (>102 cm)
Non-Asian Women*	>35 in (>88 cm)
Asian Men	>35 in (>88 cm)
Asian Women	>31 in (>80 cm)
TG	≥ 150 mg/dL or on drug tx for \uparrow TG
HDL-C	
Men	<40 mg/dL
Women	<50 mg/dL
	or on drug tx for \downarrow HDL-C
Blood pressure	≥ 130 mm Hg systolic ≥ 85 mm Hg diastolic or on HTN drug tx
Fasting glucose	≥ 100 mg/dL or on drug tx for \uparrow glucose

*Some non-Asian US adults with marginally increased circumference may be genetically predisposed to insulin resistance and other metabolic syndrome risk factors.

Grundy SM et al. *Circulation*. 2005;112.

Age-Specific Prevalence of the Metabolic Syndrome (NHANES III, 1988-94)



Ford et al. *JAMA* 287(3), p. 356-9; Jan 16, 2002

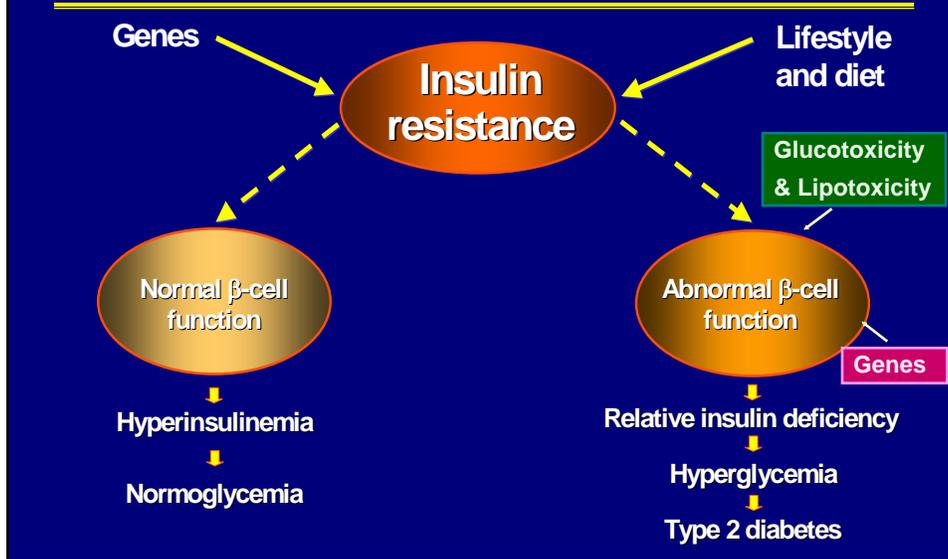
Insulin Resistance: Definition

> Insulin resistance:

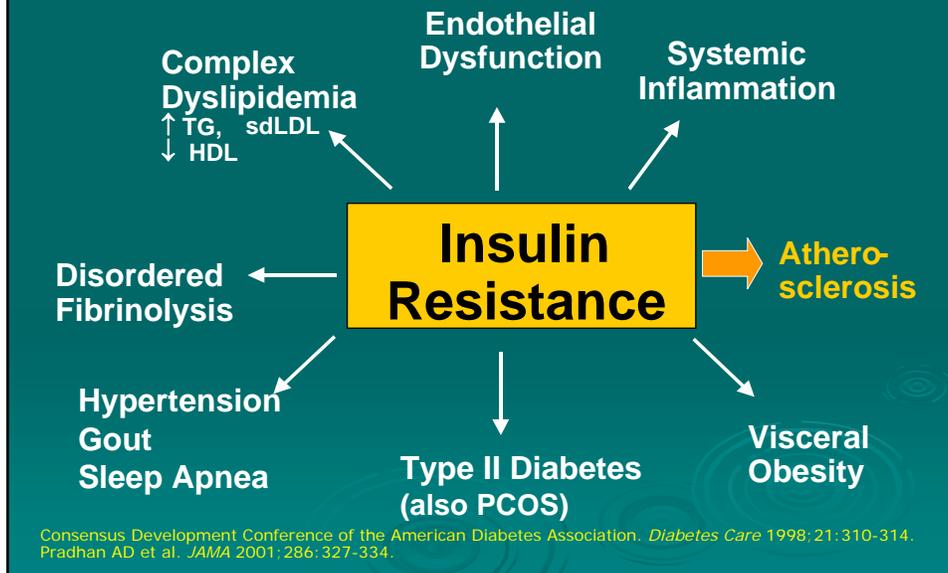
- Medical definition -- Impaired response to the physiologic effects of insulin (including those on glucose, lipid and protein metabolism), and the effects on vascular endothelial function
- Translation – Body tissues responding to insulin inefficiently such that the pancreas has to work harder to produce more insulin to meet the increased demand

Haffner SM et al, *Diabetes Care* 1999; 22: 562-568
Consensus Development Conference of the American Diabetes Association
Diabetes Care 1998; 21: 310-314

Etiology of Type 2 Diabetes: Insulin Resistance and Diminished Insulin Secretion

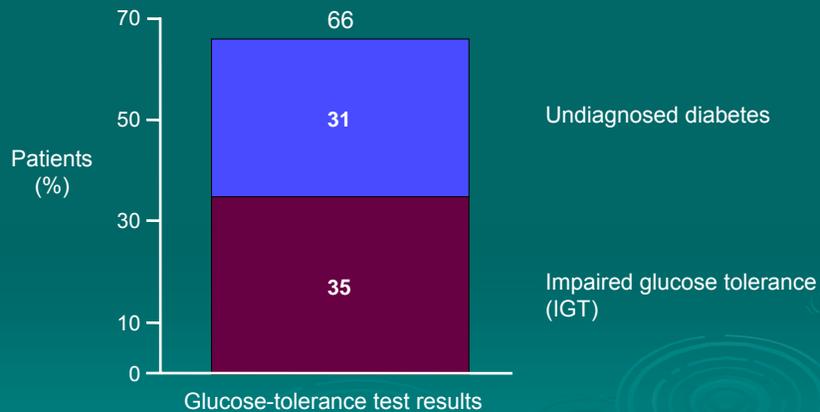


The Metabolic Syndrome of Insulin Resistance



Almost 70% of patients with first MI have IGT or undiagnosed diabetes

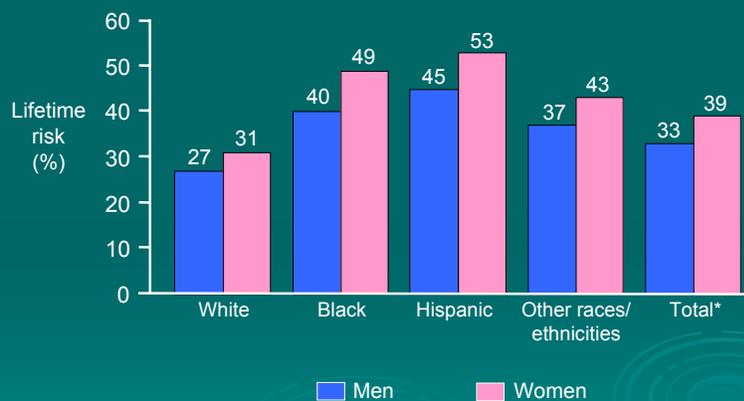
N = 181 consecutive patients admitted to CCU



Norhammar A et al. *Lancet*. 2002;359:2140-4.

Lifetime risk of diabetes for individuals born in 2000

Estimates based on National Health Interview Survey (1984–2000)



*Weighted race/ethnic-specific values by proportion of nondiabetic US population in 2000

Narayan KMV et al. *JAMA*. 2003;290:1884-90.

Obesity and Physical Inactivity in Children: A Call to Arms

- US Children
- 15% are overweight
- Due to
 - Physical inactivity
 - Caloric over-consumption
- Type 2 DM approaching Type 1 in Children
- 1/3 of all children born in 2000 will become diabetic



Therapeutic Lifestyle Modification

Pediatrics, August 2003.

Walking the Dog!!



Completed Diabetes Prevention Trials

Trial	Treatment	Relative Risk
Finnish Diabetes Prevention Study	Intensive D+E vs control	↓ 58%
Da Qing Study	D, E or D+E vs control	↓ 42%
DPP	Intensive D+E vs placebo	↓ 58%
	Metformin vs placebo	↓ 31%
STOP-NIDDM	Acarbose vs placebo	↓ 21%
Fasting Hyperglycemic study	Gliclazide or intensive lifestyle modification	No effect
TRIPOD	Troglitazone in GDM	↓ 56%

The Diabetes Prevention Program (DPP)

A Randomized Clinical Trial to Prevent Type 2 Diabetes in Persons at High Risk

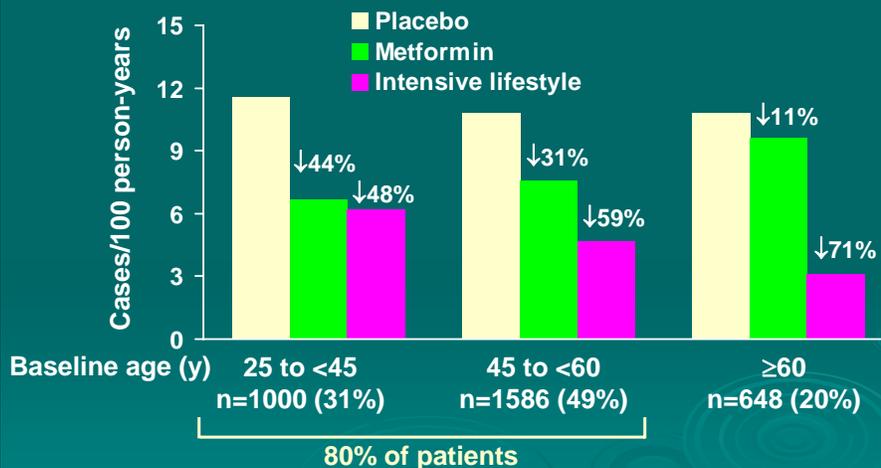
NEJM 2002;346:393-403
Diabetes Care 2000;23:1619-1629
Diabetes Care 1999;22:543-545
<http://www.bsc.gwu.edu/dpp>

Diabetes Prevention Program: Intensive Lifestyle Interventions

- Frequent sessions with a case manager, including
 - At least 16 sessions during first 24 weeks
 - Instruction in diet, exercise, and behavior modification
 - to achieve and maintain weight-loss goals by fat reduction, then calorie reduction
 - Goals:
 - $\geq 7\%$ loss of body weight and maintenance of weight loss
 - ≥ 150 minutes per week of moderate intensity physical activity
 - At least monthly contact thereafter
- Two optional, supervised exercise sessions per week
- 4–6-week group courses offered quarterly

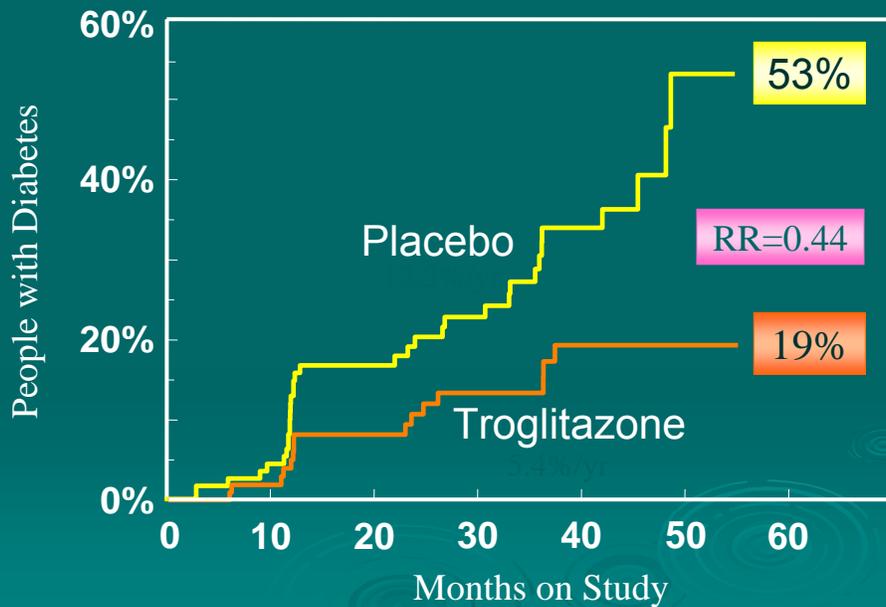
The Diabetes Prevention Program Research Group. *Diabetes Care*. 1999;22:623.

Diabetes Prevention Program: Progression to Type 2 Diabetes by Age



The Diabetes Prevention Program Research Group. *N Engl J Med*. 2002;346:393.

Preventing Diabetes: The “TRIPOD” Study



TRIPOD: Conclusion

Reducing secretory demands placed on pancreatic *B*-cells by chronic insulin resistance can delay or prevent the onset of type 2 diabetes.

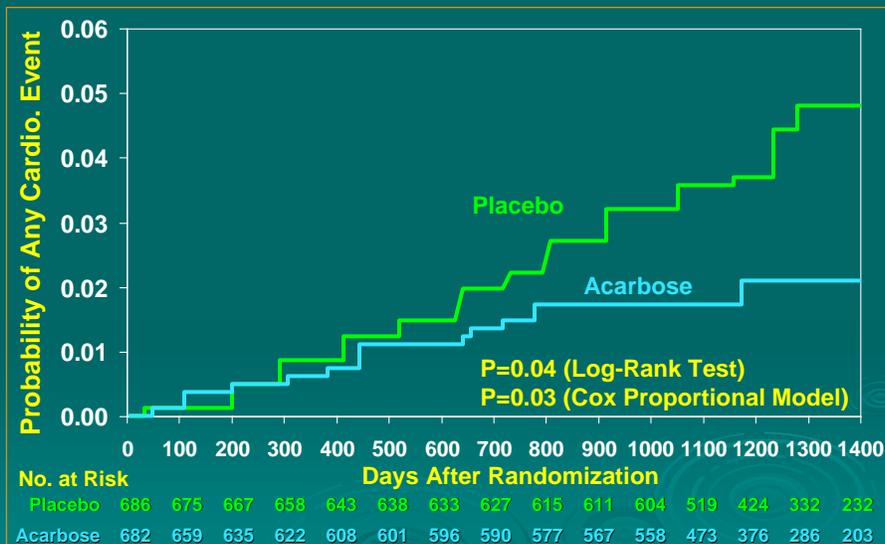
“*B*-cell rest = *B*-cell protection”

Diabetes Prevention With Pharmacologic Therapy: STOP-NIDDM

- 1418 overweight (BMI >24) individuals IGT and FPG between 101 and 140 mg/dL randomized to placebo or acarbose (50-100 mg/d)
- Average duration of follow up: 3.6 years
- Treatment with acarbose resulted in a statistically significant 33% reduction in the risk of developing diabetes

Chiasson et al. EASD 2001.

Effect of Acarbose on the Probability of Remaining Free of Cardiovascular Disease



Chiasson J. et al., JAMA 2003; 290:486-94.

Diabetes Prevention: Secondary Analysis from CV Trials

Study	Risk category	Intervention	RRR vs. controls
WOSCOPS Freeman et al, <i>Circulation</i> 2001	Age 45-64, FPG < 126, hyperlipidemia	Pravachol	- 30%
HOPE Yusuf et al, <i>NEJM</i> 2000	Age > 55 + vascular disease or DM + one other CV risk factor	Ramipril	- 34%
LIFE Dahlof et al, <i>Lancet</i> 2002	Age < 55 + hypertension and LVH	Losartan	- 25%
SOLVD Vermes et al, <i>Circulation</i> 2003	Mean age 56 with LV dysfunction (mostly ischemic)	Enalapril	Baseline IFG: - 44.7% NFG: - 10.7%

Diabetes Prevention: Other Pharmacologic Agents Studied

Study	Intervention Studied
ASCOT	Perindopril + amlodipine reduced development of diabetes vs. atenolol + diuretic
Rio Europe	Rimonabant (endocannabinoid CB1 receptor antagonist)
Xendos	Orlistat (Xenical) 120mg

Diabetes Prevention: Other Potential Strategies

- Bariatric surgery:
 - 95.6% of 645 patients reversed metabolic syndrome at 1 year
 - 17.2% in 29 nonsurgical patients vs 0% of bariatric surgery patients developed diabetes after 4 years of follow-up
 - Swedish Obese Subjects Study: reduced 2yr and 10yr diabetes rate in 1268 patients
- Exenatide (Byetta):
 - Stimulates release of insulin in response to food, reduces glucagon production and increases pancreatic beta cell (insulin-producing cells) mass

Ongoing Studies (DM Prevention)

Study	Design / treatments	Target no. of patients	Endpoints
DREAM	Ramipril vs rosiglitazone vs ramipril + rosiglitazone vs placebo)	4000 IGT	Development of diabetes
NAVIGATOR	Nateglinide vs valsartan vs nateglinide + valsartan vs placebo	9150 (IGT & age ≥ 50 with CVD or ≥ 55 with risk factors for CVD	Progression to diabetes and CV events

Should you have a Glucose Tolerance Test??

- YES!! If you have risk factors for diabetes / metabolic syndrome –
 - Overweight (BMI ≥ 25 , lower cutoff for Asian)
 - Waist circumference ≥ 35 inches in women; ≥ 40 inches in men (lower cutoff for Asians)
 - Fasting glucose 95 or above
 - Sedentary lifestyle
 - Family history of type 2 diabetes, cardiovascular disease, hypertension, dyslipidemia (esp. \uparrow triglycerides and/or \downarrow HDL)
 - Personal history of glucose intolerance or gestational diabetes (or having had children with birthweight ≥ 9 lbs)
 - Diagnosis of cardiovascular disease, hypertension, dyslipidemia, acanthosis nigricans, PCOS (polycystic ovarian syndrome), sleep apnea...
 - Taking medications that can worsen insulin resistance and increase risk of diabetes – eg. steroids, atypical antipsychotic medications...

How to Minimize Risk of Diabetes for You and Your Family

- Get appropriate testing to evaluate your cardiometabolic risk
- Healthy lifestyle
 - Nutrition
 - Exercise
 - Adequate sleep
 - Stress reduction
- Share your medical history with family members to alert them to have appropriate work-up
- If any of your family members have risk factors for diabetes or conditions associated with diabetes, be proactive, ask for a glucose tolerance test (ideally with insulin levels)!

Diabetes Prevention - Conclusion

- Diabetes Prevention requires an Integrative approach!
 - Proactive / advanced cardiometabolic risk testing
 - Nutrition
 - Exercise
 - Stress reduction / quality sleep / behavioral modification



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