Atypical Antipsychotics and Diabetes

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11 September 2003

Outline

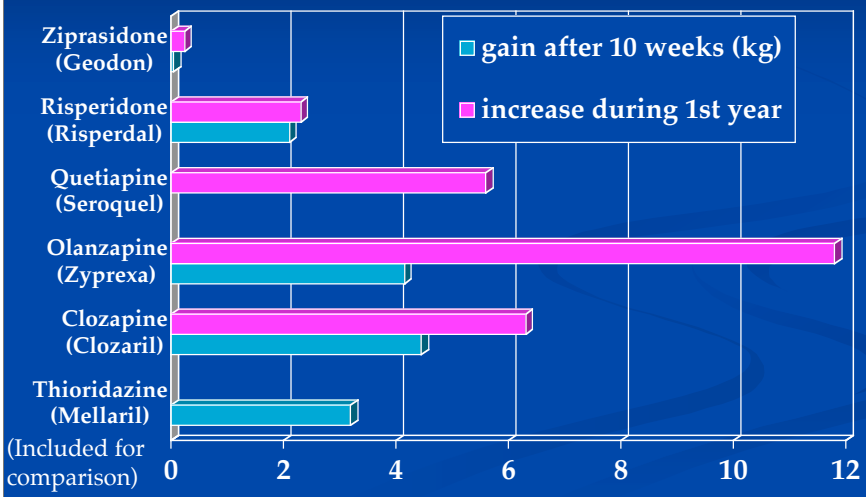
- Atypical antipsychotics (AAPs) cause weight gain and diabetes in some patients
- How can we identify which patients are at risk?
- Are there any interventions which reduce risk?

Metabolic side effects of atypical antipsychotics

- Weight gain
- Obesity
- Type 2 diabetes
- Sometimes diabetic keto-acidosis (Jin 2002)
  - Younger, female, lower baseline weight

AAPs and risk of weight gain

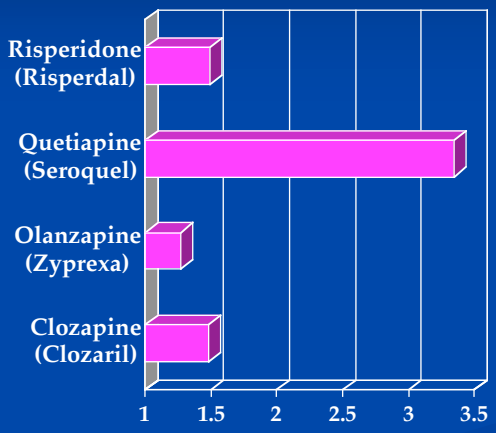
(Lebovitz 2003)



Blue bars: metaregression analysis of data from 81 studies

AAPs and risk of diabetes

(International Conference of Pharmacoepidemiology 2003)



Risk for diabetes, relative to typical antipsychotics

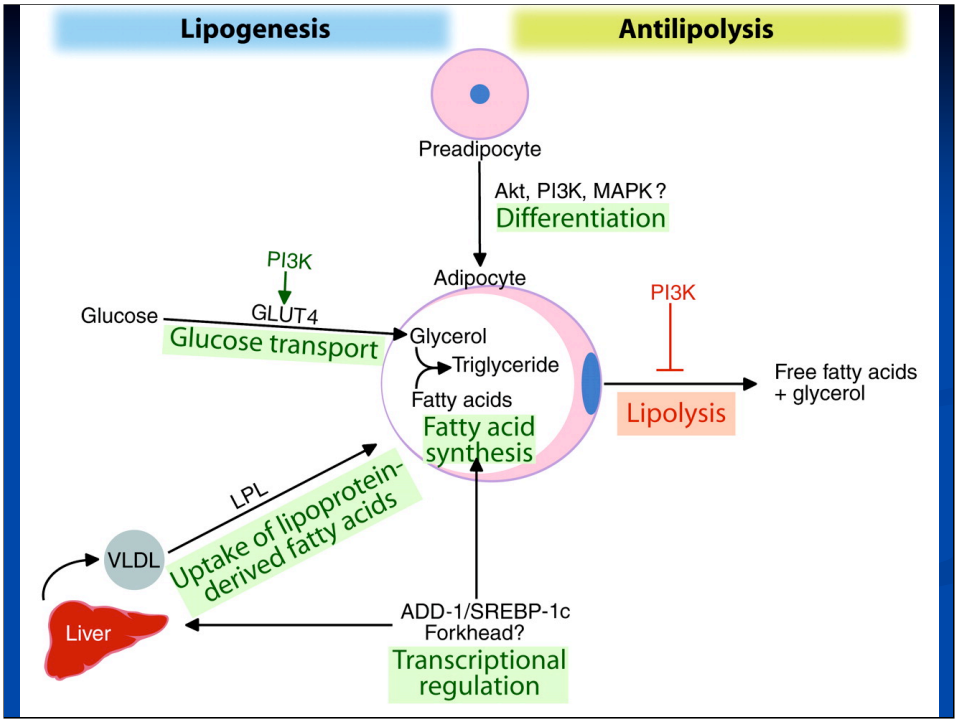
- Veteran's Health Administration study
- 12,235 patients with no prior Dx of diabetes
- 739 cases of diabetes

Diabetes type 1 vs type 2

- DM 1
  - Childhood onset
  - Insulin dependent
  - Auto-immune disorder; destruction of insulin-producing cells in the pancreas
  - Without treatment with insulin:
    - Weight loss
    - Diabetic ketoacidosis
    - death
- DM 2
  - Usually adult onset
  - 90% of cases of DM
  - 90% of DM 2 are obese
  - Insulin resistance
  - Treatments include diet, oral hypoglycemic agents, sometimes insulin
  - Epidemic
  - Complications may be due to too much insulin

How does weight gain occur?

- Action of insulin


Lipogenesis
Antilipolysis
Preadipocyte
Akt, PI3K, MAPK?
Differentiation
PI3K
Adipocyte
Glucose
GLUT4
Glucose transport
Glycerol
Triglyceride
Fatty acids
Fatty acid synthesis
PI3K
Lipolysis
Free fatty acids + glycerol
LPL
Uptake of lipoprotein-derived fatty acids
VLDL
Liver
ADD-1/SREBP-1c
Forkhead?
Transcriptional regulation

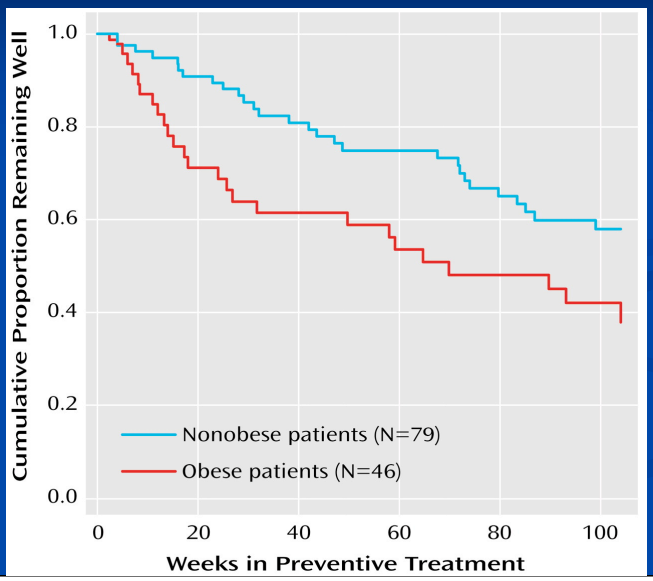
AAPs increase insulin levels

- Hyperinsulinemia in pts on olanzapine
  - 10 / 14 patients (Melkersson 2000)
  - 4 / 11 patients (Cohn 2002)

Which patients are most at risk?

- Those who already have high insulin levels
  - Due to higher levels of secretion
  - Lower rates of insulin breakdown
  - A combination of the two
- Genetic predisposition
- Bipolar patients are more likely to be obese, especially depressed bipolars
  - 32% of 50 consecutive bipolar I patients had BMI > 30 (Fagiolini 2002)
- Schizophrenic patients are more likely to have DM 2 (2-3 times risk of general population Lebovitz 2003)

Bipolar patients who are obese have a worse course of illness (Fagiolini 2003)

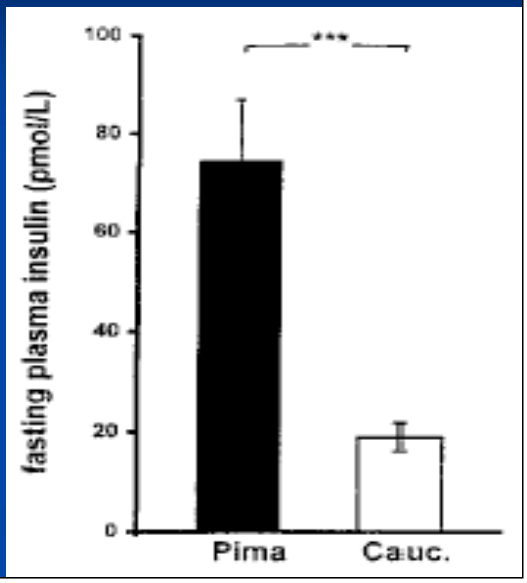


Who has this genetic predisposition to high insulin levels?

- Aboriginals
  - Pima Indian children have higher fasting insulin levels than Caucasian children of similar age and weight (Pettitt 1993)

Genetic predisposition

- Another study comparing age and gender-matched Pima Indian & Caucasian children (Weyer 2001)
- Pima children were heavier (BMI 20.1 vs 15.4)



Genetic predisposition

- in African-American children, family history of type 2 diabetes is a risk factor for insulin resistance (Danadian 1999)
- A Canadian study (Katzmarzyk 2000) comparing risks of obesity in spouses and first degree relatives of obese probands showed higher risk for relatives compared to spouses.

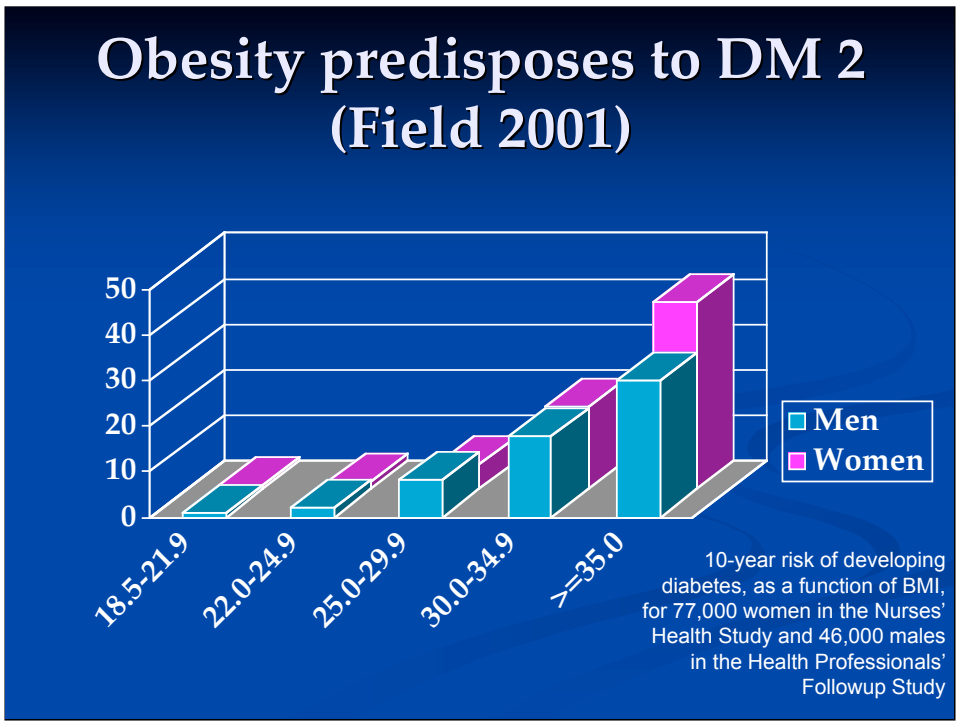
The "Thrifty gene" hypothesis

- Typical diet in pre-agrarian days was low in carbohydrates
- Weight gain prior to winter had survival value
- The agrarian revolution made carbohydrates available year-round
- The thrifty gene causes obesity with year-round carbohydrates
- Thrifty gene now in only a fraction of the population

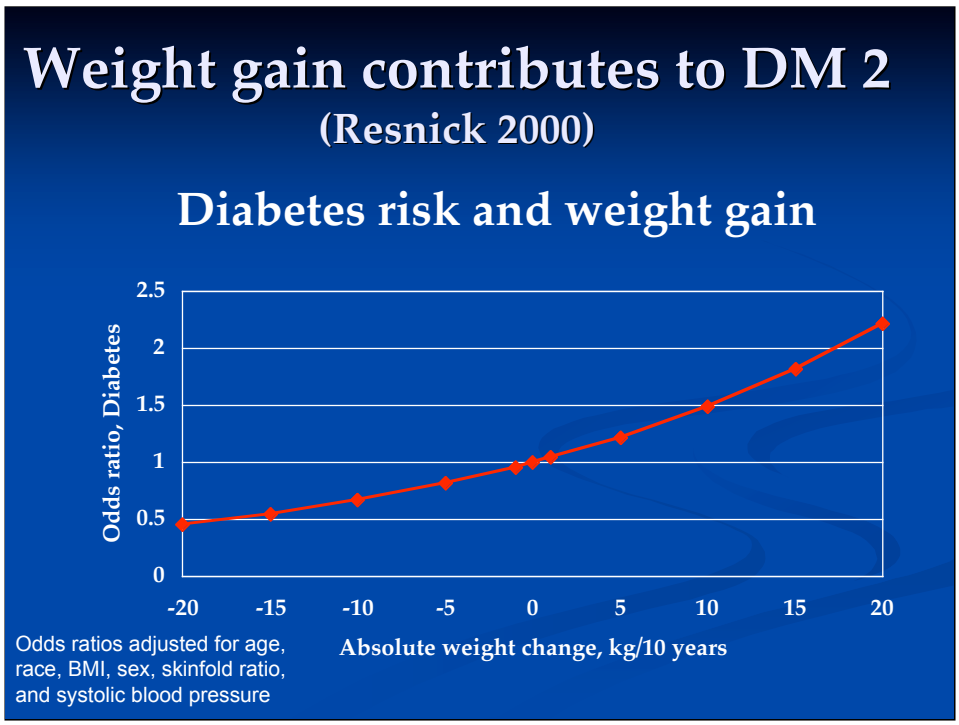
The thrifty gene and diabetes

- High-carbohydrate diet leads to high insulin levels
- High insulin = weight gain
  - Especially central adiposity
- Obesity causes insulin resistance (Kahn 2000)

This is where we discuss our different view of genesis of tytype 2 diabetes.



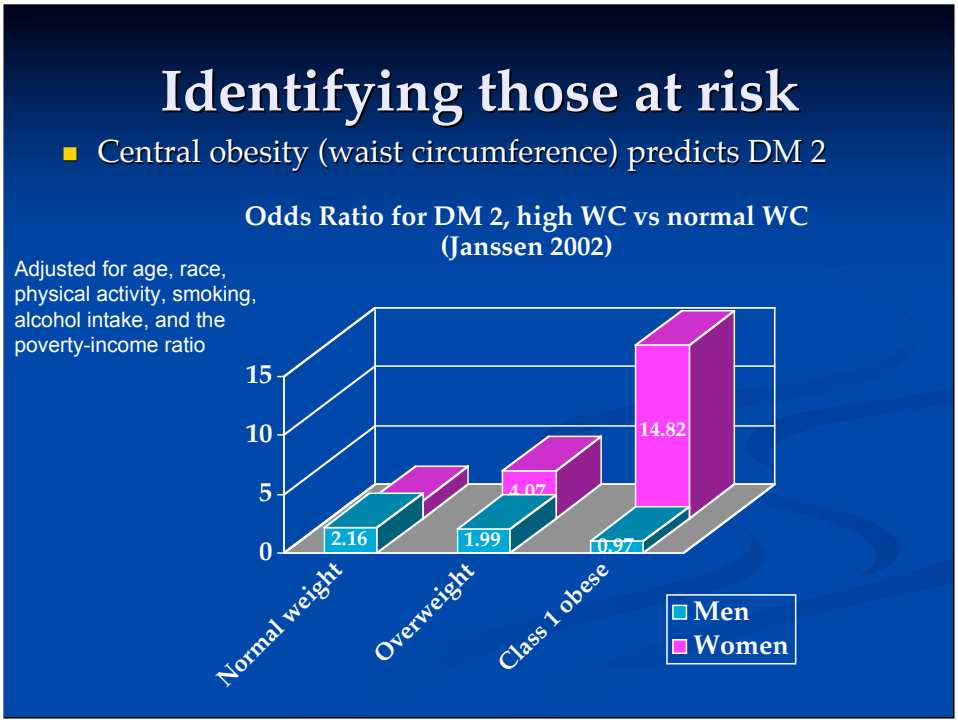
10-year risk of developing diabetes, as a function of BMI, for 77,000 women in the Nurses' Health Study and 46,000 males in the Health Professionals' Followup Study.



Odds ratios adjusted for age, race, BMI, sex, skinfold ratio, and systolic blood pressure.

The thrifty gene and diabetes (2)

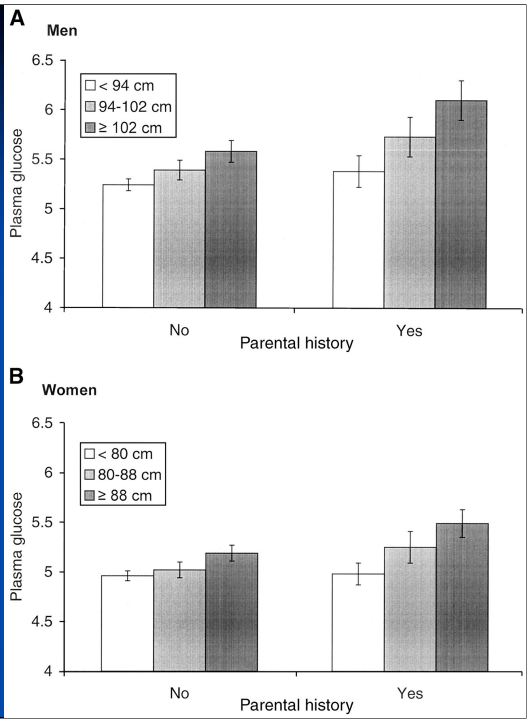
- Insulin resistance reduces further weight gain
- Diabetes contributes to weight loss by calorie loss (Ludwig 2002)
  - Homeostatic mechanism vs pathology
- Weight loss increases insulin sensitivity (Brochu 2003)



Adjusted for age, race, physical activity, smoking, alcohol intake, and the poverty-income ratio.

Identifying those at risk

- Family history of DM 2 (van Dam 2001)
- Stronger association between abdominal obesity(waist circumference) and higher plasma glucose in individuals who had a parental history of diabetes than in those who did not

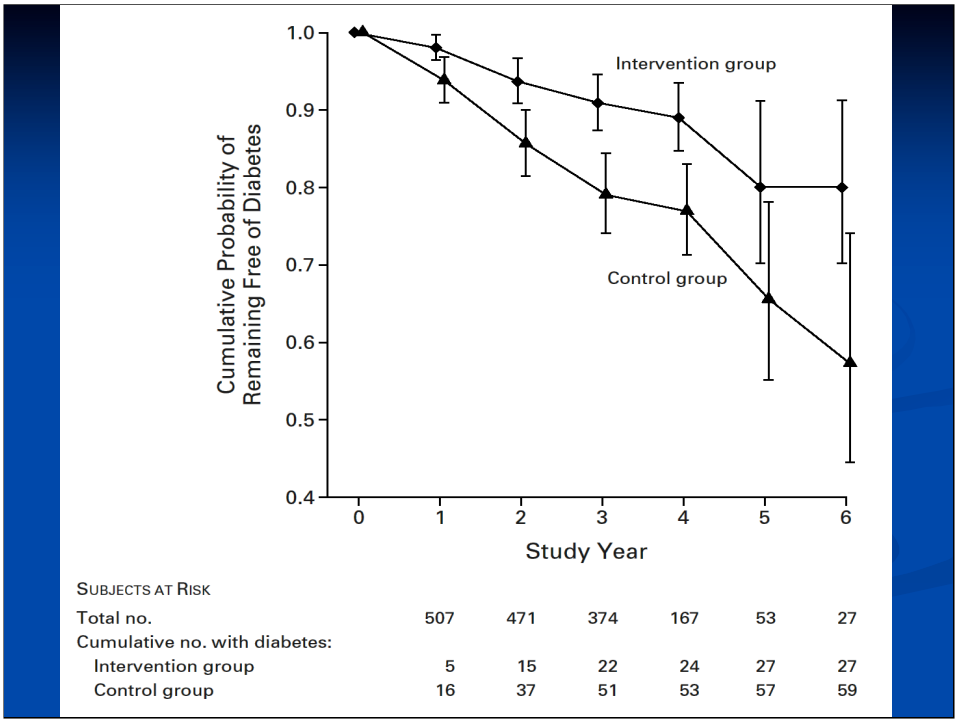


What can be done to reduce the risk of diabetes in patients taking atypical antipsychotics?

Weight loss can reduce the incidence of diabetes
(Pinkney 2002)

Example: weight loss

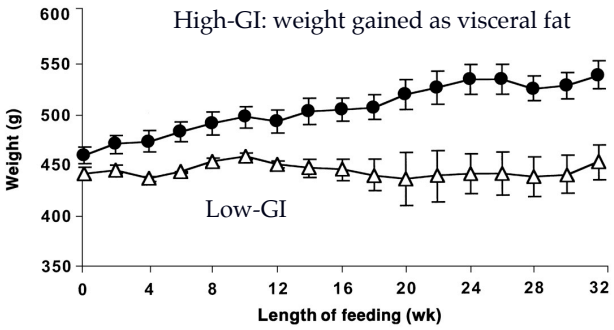
- Tuomilehto 2001:
- 522 middle-aged overweight patients with impaired glucose tolerance were randomized
- Intervention group received individualized counseling to:
  - Reduce weight
  - Reduce total fat intake
  - Reduce saturated fat intake
  - Increase dietary fibre
  - Increase physical activity
- After 1 year:
  - weight loss 4.2 kg vs 0.8 kg
  - Waist circumference reduction 4.4 cm vs 1.3 cm



Subjects at Risk						
Total no.	507	471	374	167	53	27
Cumulative no. with diabetes:						
Intervention group	5	15	22	24	27	27
Control group	16	37	51	53	57	59

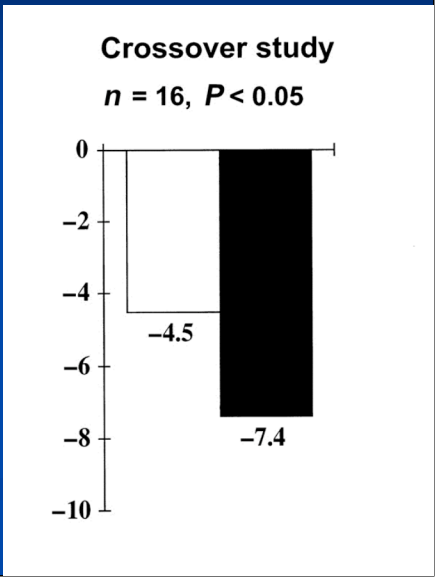
Prevent weight gain: low GI

- Low glycemic index meals
  - No weight gain in rats fed isoenergetic low-GI, vs high-GI diet (Brand-Miller 2002)



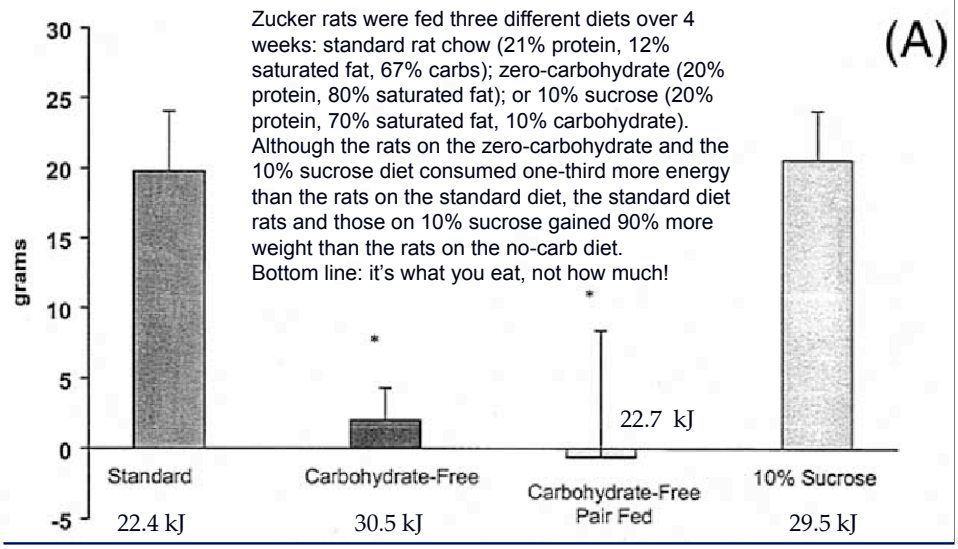
Weight loss with low GI

- Low glycemic index meals
  - Promote weight loss
    - Weight loss in pounds for overweight women randomly assigned to high-glycemic index (white) or low GI diet (black). Diets equal in calories. (Slabber 1994)
  - The Montignac diet is based on low-GI principles



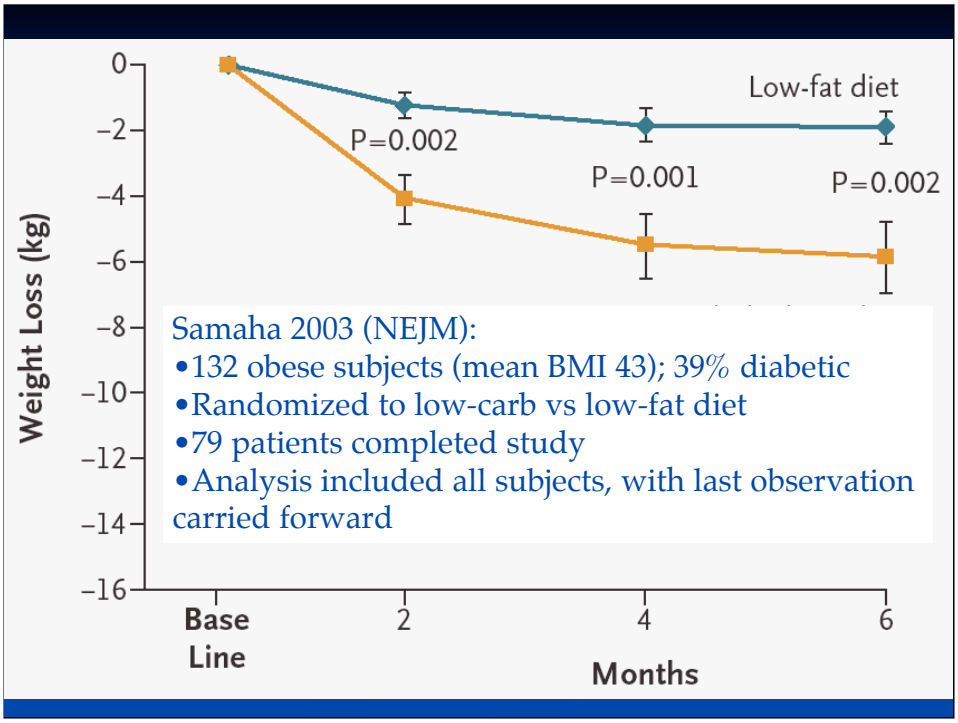
Reduce carbohydrates

(Morris 2003)



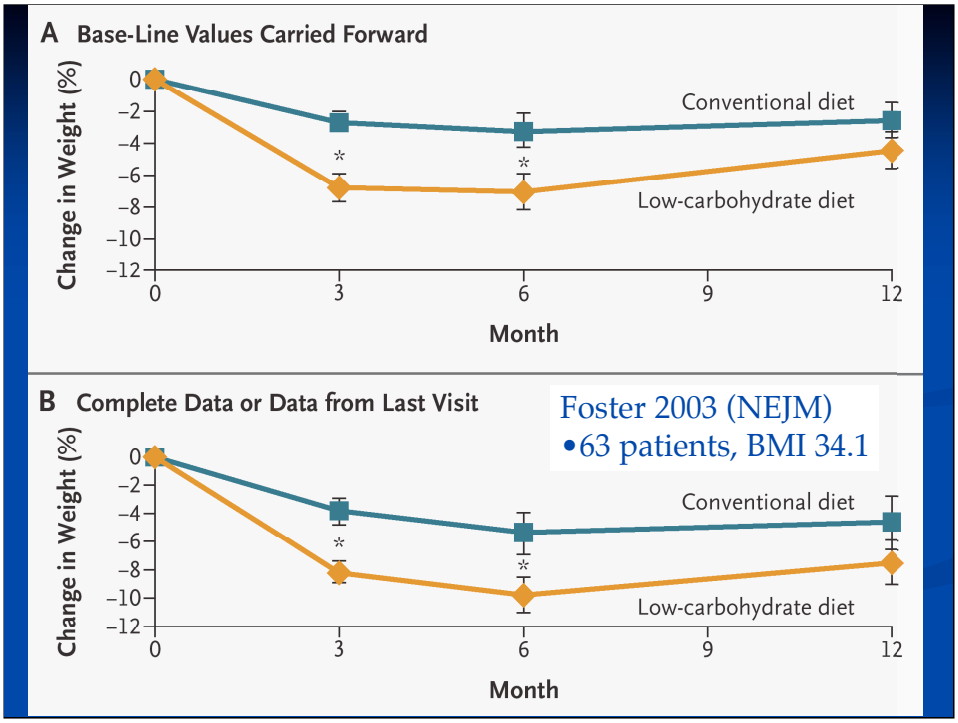
Zucker rats were fed three different diets over 4 weeks: standard rat chow (21% protein, 12% saturated fat, 67% carbs); zero-carbohydrate (20% protein, 80% saturated fat); or 10% sucrose (20% protein, 70% saturated fat, 10% carbohydrate). Although the rats on the zero-carbohydrate and the 10% sucrose diet consumed one-third more energy than the rats on the standard diet, the standard diet rats and those on 10% sucrose gained 90% more weight than the rats on the no-carb diet.
Bottom line: it's what you eat, not how much!

Low-carb (Dr. Atkins) diet



Samaha 2003 (NEJM):

- 132 obese subjects (mean BMI 43); 39% diabetic
- Randomized to low-carb vs low-fat diet
- 79 patients completed study
- Analysis included all subjects, with last observation carried forward



Foster 2003 (NEJM)
- 63 patients, BMI 34.1

Attempts to ban Atkins diet

- Norfolk and Norwich Hospital in Britain has banned Atkins diet from its menus, citing safety concerns
- Physicians Committee for Responsible Medicine in the U.S. is urging hospitals, eg Johns Hopkins & Mayo Clinic, to adopt a similar ban