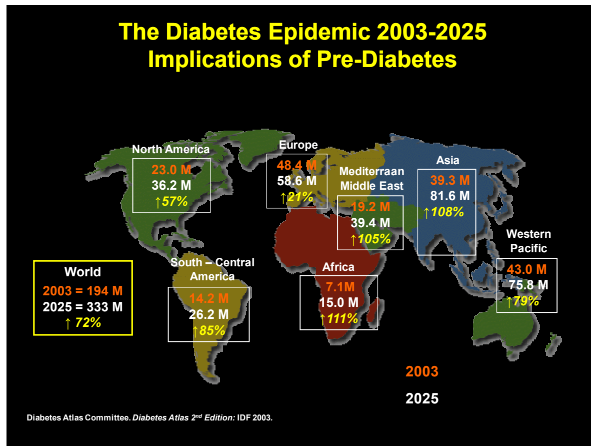
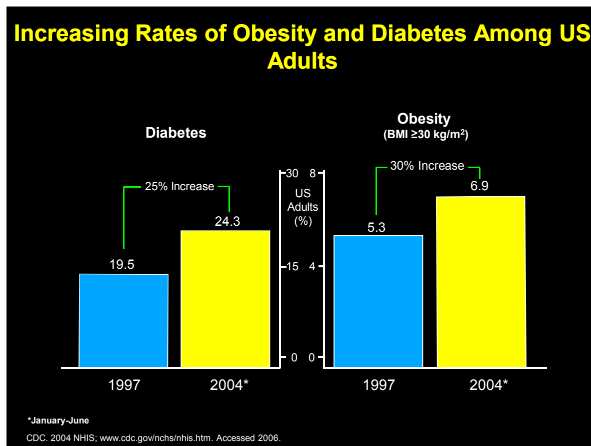
Obesity as a Target for Management of Diabetes

Carol Hatch Wysham, MD
Clinical Assistant Professor of Medicine
University of Washington School of Medicine
Rockwood Clinic
Spokane, WA

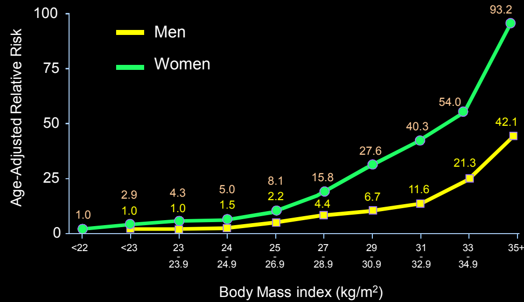




Obesity in the Setting of Type 2 Diabetes

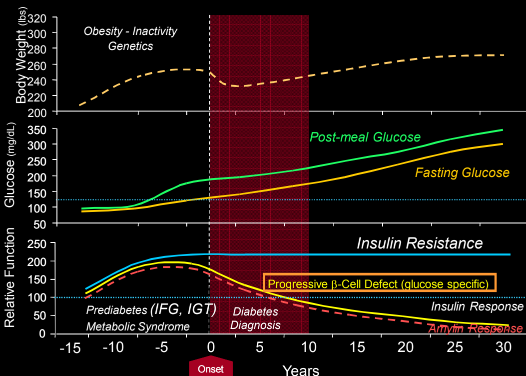
- Obesity and T2DM tightly linked
  - Independent risk factor for development of diabetes
  - Weight gain generally precedes development of diabetes
  - Common co-morbidities
- Cardiometabolic risk tied to both obesity and diabetes
  - Cluster of common CVD risk factors
- Management of obesity in individuals with type 2 diabetes
  - Benefit of intensive lifestyle management
  - Pharmacologic therapy
  - Emerging role of “weight advantageous” diabetes therapies

Relationship Between Increasing BMI and Risk of Type 2 Diabetes

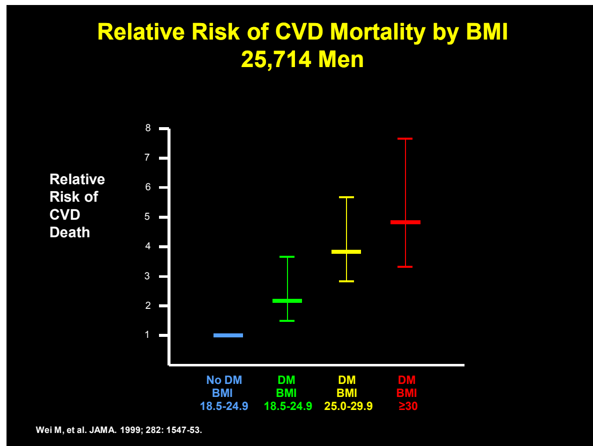


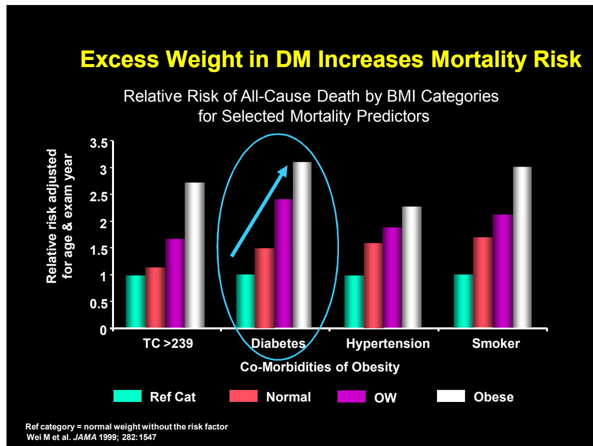
Chan J et al. *Diabetes Care* 1994;17:961.
Colditz G et al. *Ann Intern Med* 1995;122:481.

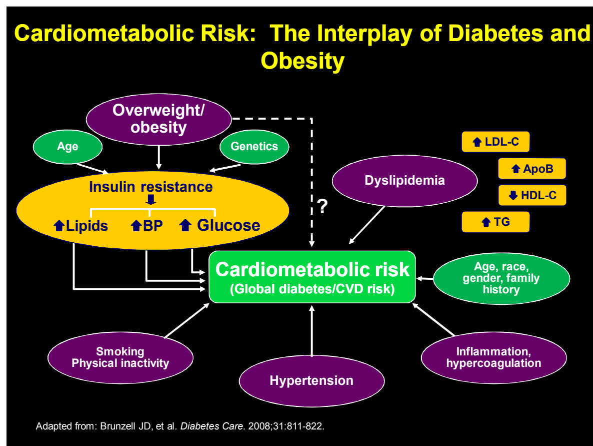
Natural History of Type 2 Diabetes and Obesity

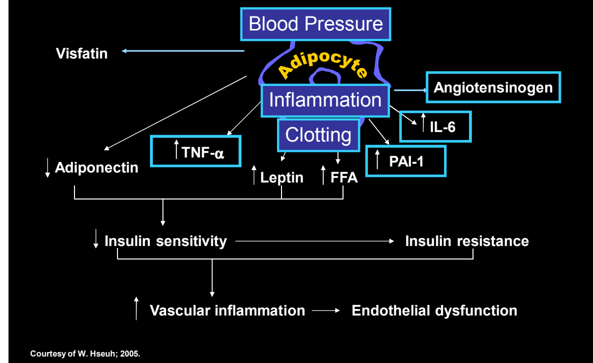


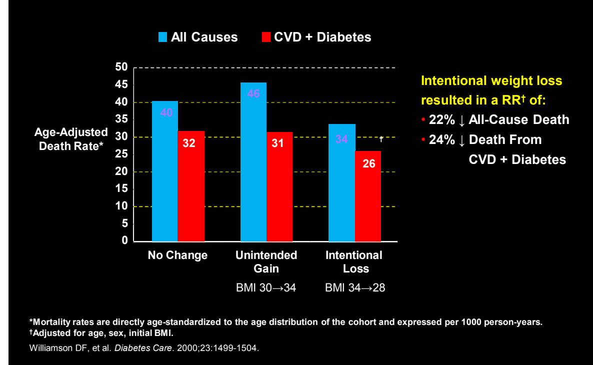
Adapted from Kendall DM, et al. © 2004 International Diabetes Center, Minneapolis, MN. All rights reserved.


Relative Risk of CVD Mortality by BMI
25,714 Men
Relative Risk of CVD Death
8
7
6
5
4
3
2
1
No DM BMI 18.5-24.9
DM BMI 18.5-24.9
DM BMI 25.0-29.9
DM BMI ≥30
Wei M, et al. JAMA. 1999; 282: 1547-53.


Excess Weight in DM Increases Mortality Risk
Relative Risk of All-Cause Death by BMI Categories
for Selected Mortality Predictors
Relative risk adjusted for age & exam year
3.5
3
2.5
2
1.5
1
0.5
0
TC >239
Diabetes
Hypertension
Smoker
Co-Morbidities of Obesity
Ref Cat
Normal
OW
Obese
Ref category = normal weight without the risk factor
Wei M et al. JAMA 1999; 282:1547


Cardiometabolic Risk: The Interplay of Diabetes and Obesity
Overweight/ obesity
Age
Genetics
Insulin resistance
↑Lipids
↑BP
↑ Glucose
?
Dyslipidemia
↑ LDL-C
↑ ApoB
↓ HDL-C
↑ TG
Cardiometabolic risk
(Global diabetes/CVD risk)
Age, race, gender, family history
Smoking
Physical inactivity
Hypertension
Inflammation, hypercoagulation
Adapted from: Brunzell JD, et al. Diabetes Care. 2008;31:811-822.





Rx for Weight Loss: Hippocrates

- "…those desiring to lose weight should perform hard work before food"
- "No other refreshement except only wine"
- "Food should be of fatty nature . . . "
- "Eat only once a day"
- "Take no baths"
- "Sleep on a hard bed"
- "Walk naked as long as possible"

Works of Hippocrates, 1338, by Alexios Apokaukos.
Christopoulou-Aletra and Papavramidou. World J. Surg. 28, 513–517, 2004

12

Lifestyle Modification is Important

13

One Pound of Fat

- How many "Big Macs" would you have to eat to gain one pound of fat?
- How many Grande White Chocolate Mochas?
- How many miles would a 200 pound person have to walk to lose one pound of fat?

Easy on, but no easy off!!

14

Look AHEAD
Study Objective and Design

- Objective: Examine the long-term effects of an Intensive Lifestyle Intervention (ILI) on the incidence of major cardiovascular disease events

N=5,145
Age 45-74 with Type 2 Diabetes and a BMI >25 kg/m^2

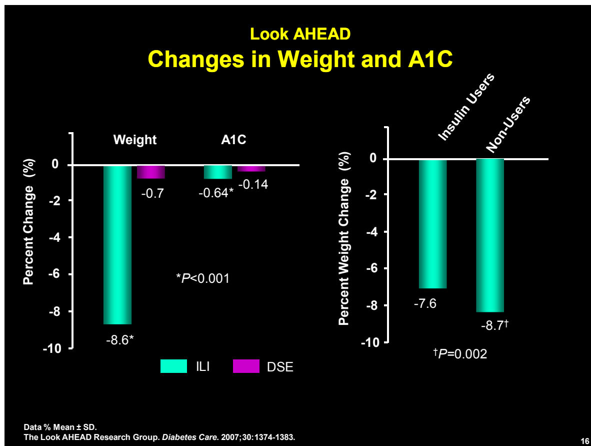
2-Week Prerandomization
- Self monitoring of diet and physical activity
- 1 diabetes education session

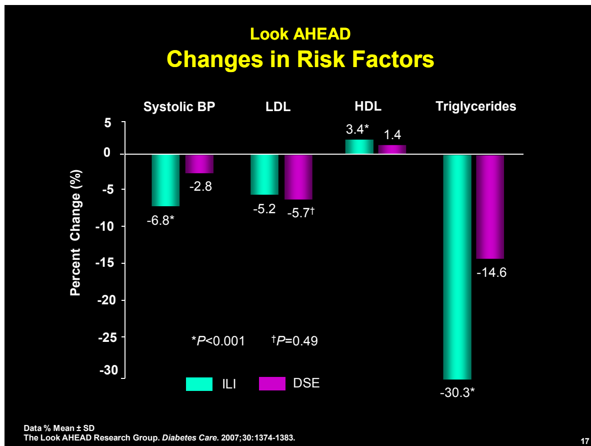
Intensive Lifestyle Intervention (ILI)
- Toolbox Approach
  - Diet modification and caloric restriction
  - Increased physical activity
  - Weekly followed by bi-monthly group meetings
  - Monthly one-on-one counseling sessions

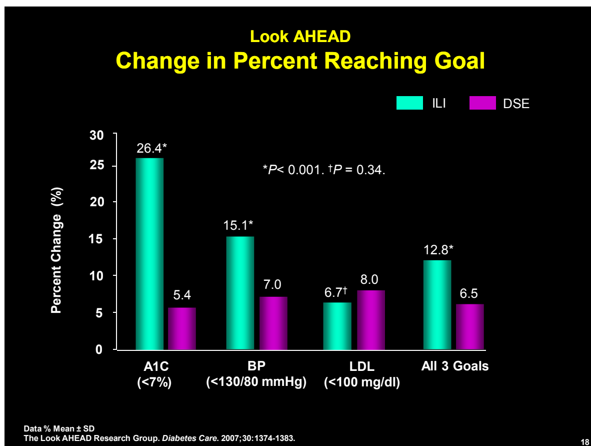
Diabetes Support and Education (DSE)
- Access to 3 additional group education sessions
- No weigh-in at meetings and no behavioral strategy counseling

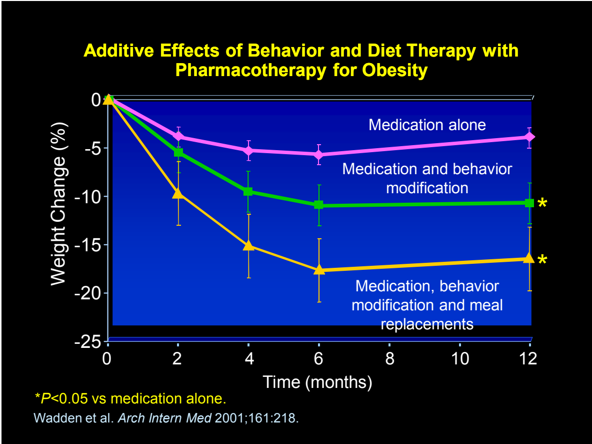
The Look AHEAD Research Group. *Diabetes Care.* 2007;30:1374-1383.

15

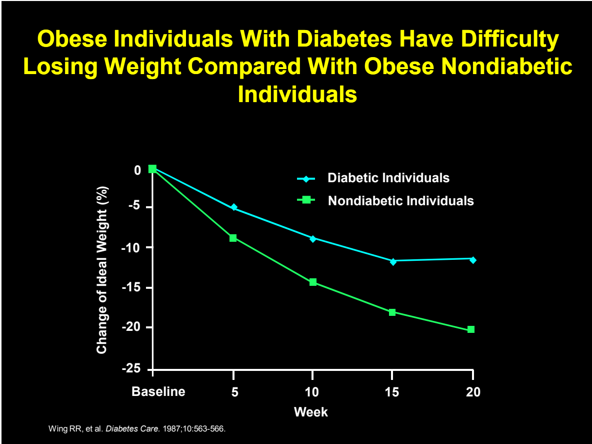

Look AHEAD
Changes in Weight and A1C
Weight
A1C
Percent Change (%)
0
-2
-4
-6
-8
-10
-0.7
-0.64*
-0.14
*P<0.001
-8.6*
ILI
DSE
Insulin Users
Non-Users
Percent Weight Change (%)
-7.6
-8.7†
†P=0.002
Data % Mean ± SD.
The Look AHEAD Research Group. Diabetes Care. 2007;30:1374-1383.
16


Look AHEAD
Changes in Risk Factors
Systolic BP
LDL
HDL
Triglycerides
Percent Change (%)
5
0
-5
-10
-15
-20
-25
-30
3.4*
1.4
-2.8
-6.8*
-5.2
-5.7†
-14.6
-30.3*
*P<0.001
†P=0.49
ILI
DSE
Data % Mean ± SD
The Look AHEAD Research Group. Diabetes Care. 2007;30:1374-1383.
17

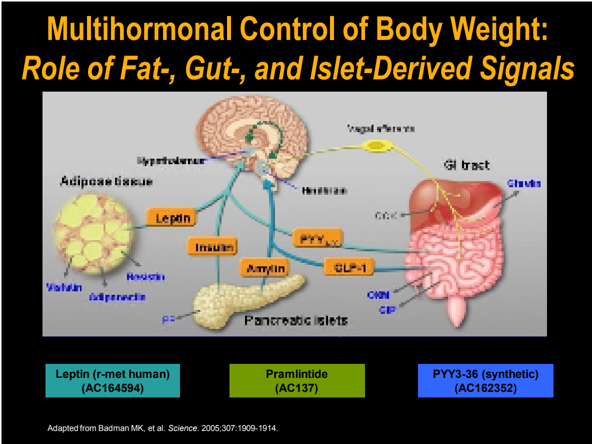

Look AHEAD
Change in Percent Reaching Goal
ILI
DSE
Percent Change (%)
30
25
20
15
10
5
0
26.4*
5.4
15.1*
7.0
6.7†
8.0
12.8*
6.5
*P< 0.001. †P = 0.34.
A1C (<7%)
BP (<130/80 mmHg)
LDL (<100 mg/dl)
All 3 Goals
Data % Mean ± SD
The Look AHEAD Research Group. Diabetes Care. 2007;30:1374-1383.
18



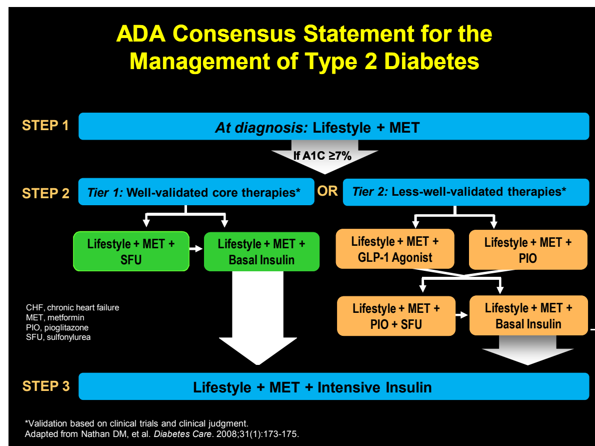
Additive Effects of Behavior and Diet Therapy with Pharmacotherapy for Obesity
Weight Change (%)
0
-5
-10
-15
-20
-25
Medication alone
Medication and behavior modification
Medication, behavior modification and meal replacements
*
*
0
2
4
6
8
10
12
Time (months)
*P<0.05 vs medication alone.
Wadden et al. Arch Intern Med 2001;161:218.

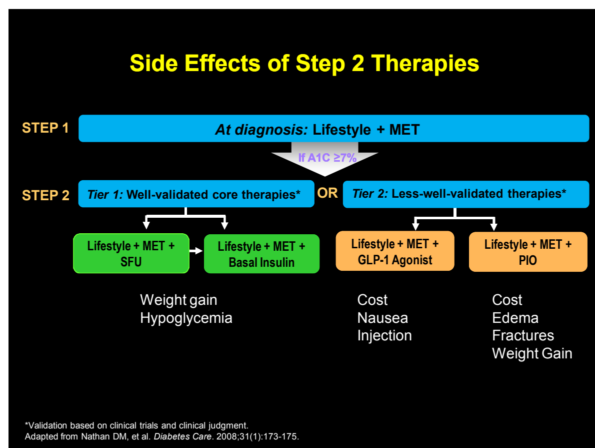


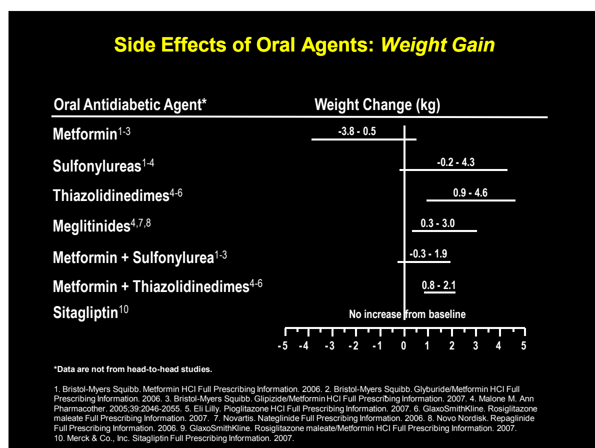
Obese Individuals With Diabetes Have Difficulty Losing Weight Compared With Obese Nondiabetic Individuals
Change of Ideal Weight (%)
0
-5
-10
-15
-20
-25
Diabetic Individuals
Nondiabetic Individuals
Baseline
5
10
15
20
Week
Wing RR, et al. Diabetes Care. 1987;10:563-566.



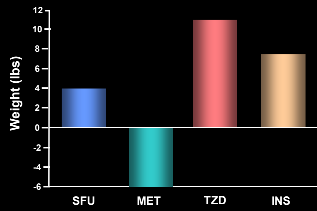
Multihormonal Control of Body Weight:
Role of Fat-, Gut-, and Islet-Derived Signals
Adipose tissue
Leptin
Insulin
Amylin
GLP-1
GI tract
Pancreatic islets
Leptin (r-met human) (AC164594)
Pramlintide (AC137)
PYY3-36 (synthetic) (AC162352)
Adapted from Badman MK, et al. Science. 2005;307:1909-1914.


ADA Consensus Statement for the Management of Type 2 Diabetes
STEP 1
At diagnosis: Lifestyle + MET
If A1C ≥7%
STEP 2
Tier 1: Well-validated core therapies*
OR
Tier 2: Less-well-validated therapies*
Lifestyle + MET + SFU
Lifestyle + MET + Basal Insulin
Lifestyle + MET + GLP-1 Agonist
Lifestyle + MET + PIO
Lifestyle + MET + PIO + SFU
Lifestyle + MET + Basal Insulin
CHF, chronic heart failure
MET, metformin
PIO, pioglitazone
SFU, sulfonylurea
STEP 3
Lifestyle + MET + Intensive Insulin
*Validation based on clinical trials and clinical judgment.
Adapted from Nathan DM, et al. Diabetes Care. 2008;31(1):173-175.


Side Effects of Step 2 Therapies
STEP 1
At diagnosis: Lifestyle + MET
If A1C ≥7%
STEP 2
Tier 1: Well-validated core therapies*
OR
Tier 2: Less-well-validated therapies*
Lifestyle + MET + SFU
Lifestyle + MET + Basal Insulin
Lifestyle + MET + GLP-1 Agonist
Lifestyle + MET + PIO
Weight gain
Hypoglycemia
Cost
Nausea
Injection
Cost
Edema
Fractures
Weight Gain
*Validation based on clinical trials and clinical judgment.
Adapted from Nathan DM, et al. Diabetes Care. 2008;31(1):173-175.


Side Effects of Oral Agents: Weight Gain
Oral Antidiabetic Agent*
Weight Change (kg)
Metformin1-3
-3.8 - 0.5
Sulfonylureas1-4
-0.2 - 4.3
Thiazolidinedimes4-6
0.9 - 4.6
Meglitinides4,7,8
0.3 - 3.0
Metformin + Sulfonylurea1-3
-0.3 - 1.9
Metformin + Thiazolidinedimes4-6
0.8 - 2.1
Sitagliptin10
No increase from baseline
-5 -4 -3 -2 -1 0 1 2 3 4 5
*Data are not from head-to-head studies.
1. Bristol-Myers Squibb. Metformin HCl Full Prescribing Information. 2006. 2. Bristol-Myers Squibb. Glyburide/Metformin HCl Full Prescribing Information. 2006. 3. Bristol-Myers Squibb. Glipizide/Metformin HCl Full Prescribing Information. 2007. 4. Malone M. Ann Pharmacother. 2005;39:2046-2055. 5. Eli Lilly. Pioglitazone HCl Full Prescribing Information. 2007. 6. GlaxoSmithKline. Rosiglitazone maleate Full Prescribing Information. 2007. 7. Novartis. Nateglinide Full Prescribing Information. 2006. 8. Novo Nordisk. Repaglinide Full Prescribing Information. 2006. 9. GlaxoSmithKline. Rosiglitazone maleate/Metformin HCl Full Prescribing Information. 2007.
10. Merck & Co., Inc. Sitagliptin Full Prescribing Information. 2007.

Weight Changes With Therapies for Type 2 Diabetes



Retrospective review 1996-2002.
N=9546 started and kept on stable therapy for at least 12 months.
Predictors of weight gain: younger age, male gender, higher A1c, use of SSRI.

Nichols GA, et al: Presented at 65th Annual Session of ADA, San Diego, June 2005.

"It all started when my doctor put me on insulin"

Weight gain with insulin treatment

- Correlates with insulin dose
- Mean weight gain 3.2 - 4.4 kg per 1% reduction in A1c
- About 2/3 adipose tissue and 1/3 lean body mass

Potential Causes of Weight Gain with Treatment of Type 2 Diabetes

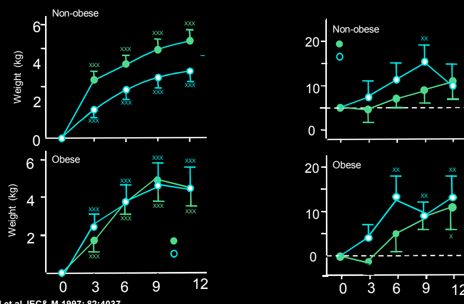
- Improved Glycemic Control
- Fear of or treatment of hypoglycemia
- Increased appetite
- Catch up from weight loss pretreatment
- Weight gain with insulin treatment
  - Correlates with insulin dose
  - Mean weight gain 3.2 - 4.4 kg per 1% reduction in A1c
  - About 2/3 adipose tissue and 1/3 lean body mass

Westphal S and Palumbo P. Insulin 2007;2:31

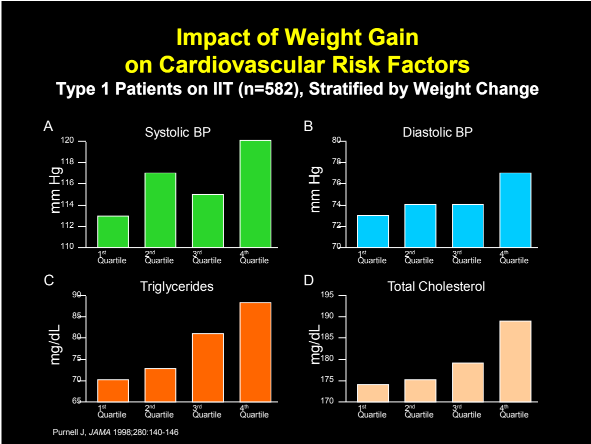
Treatment-Induced Weight Gain

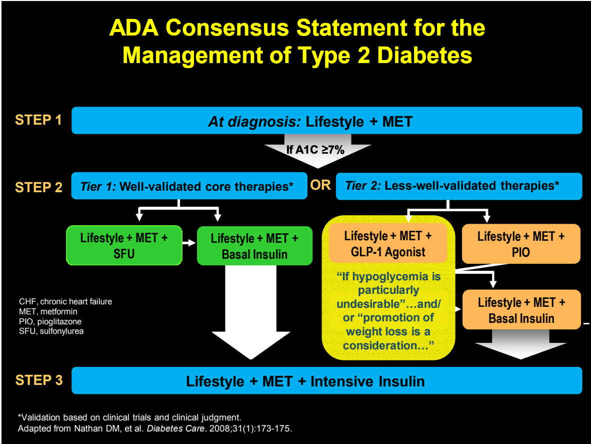
- Is weight gain from antihyperglycemic therapies the "price paid" for the improved control of hyperglycemia?
- Will patients accept weight gain?
  - It may be a barrier to compliance
  - It may discourage patients
  - It appears to be a concern for physicians
  - Glycemic goals may not be reached
- What is the impact of weight gain upon vascular complications?

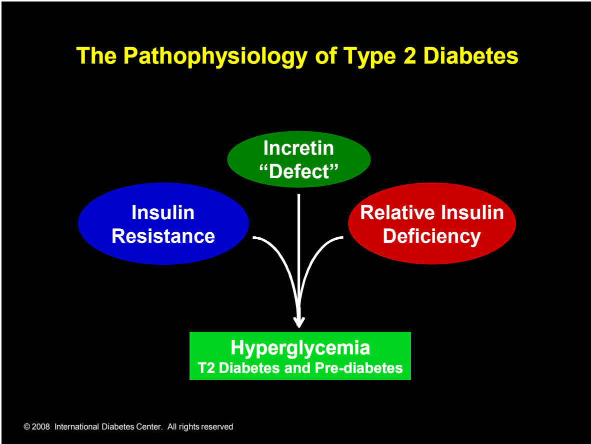
Systolic Blood Pressure Increases With Weight Gain in Type 2 Diabetes Treated With Insulin

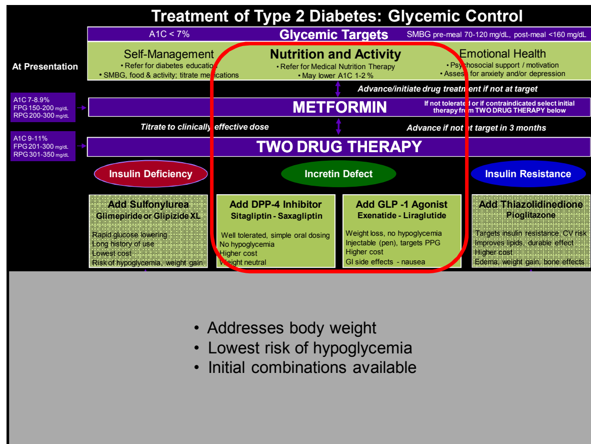


Yki-Jarvinen H et al JEC& M 1997; 82:4037


Impact of Weight Gain
on Cardiovascular Risk Factors
Type 1 Patients on IIT (n=582), Stratified by Weight Change
A
Systolic BP
mm Hg
B
Diastolic BP
mm Hg
C
Triglycerides
mg/dL
D
Total Cholesterol
mg/dL
1st Quartile
2nd Quartile
3rd Quartile
4th Quartile
Purnell J. JAMA 1998;280:140-146


ADA Consensus Statement for the
Management of Type 2 Diabetes
STEP 1
At diagnosis: Lifestyle + MET
If A1C ≥7%
STEP 2
Tier 1: Well-validated core therapies*
OR
Tier 2: Less-well-validated therapies*
Lifestyle + MET + SFU
Lifestyle + MET + Basal Insulin
Lifestyle + MET + GLP-1 Agonist
Lifestyle + MET + PIO
"If hypoglycemia is particularly undesirable"…and/ or "promotion of weight loss is a consideration…"
Lifestyle + MET + Basal Insulin
CHF, chronic heart failure
MET, metformin
PIO, pioglitazone
SFU, sulfonylurea
STEP 3
Lifestyle + MET + Intensive Insulin
*Validation based on clinical trials and clinical judgment.
Adapted from Nathan DM, et al. Diabetes Care. 2008;31(1):173-175.


The Pathophysiology of Type 2 Diabetes
Incretin "Defect"
Insulin Resistance
Relative Insulin Deficiency
Hyperglycemia
T2 Diabetes and Pre-diabetes
© 2008 International Diabetes Center. All rights reserved



Why WAIT Program

- 12 week program
  - Dietary Instruction
  - Exercise
  - Cognitive Behavioral Therapy
  - Group Education Sessions
- Medication adjustment
  - To those with favorable weight profile
    - 21% on RAI - able to D/C
    - 55% reduction in daily dose of basal insulin
    - 2/3 stopped SU
    - 13 on OA - added exenatide
    - 9 on prandial insulin - added pramlintide
    - Average cost savings for meds $140.34/pt

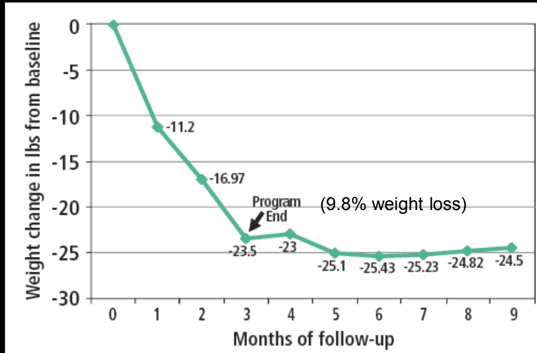
Mean weight loss - 24.6 lbs
Waist circumference - -3.7"

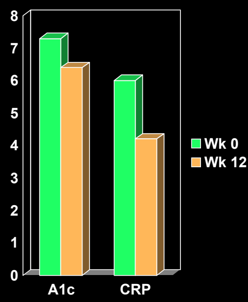
Hamdy, O. Presented at the 68th Annual Scientific Sessions of the American Diabetes Association 2008

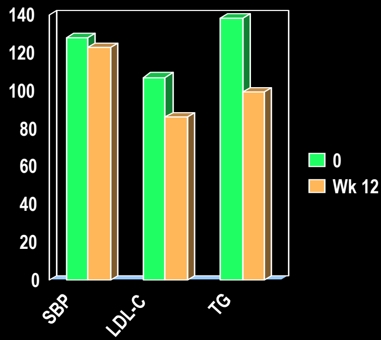
Antihyperglycemic Medications

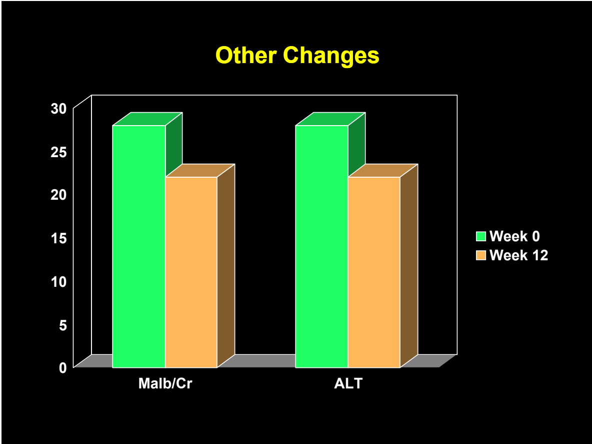
Weight unfriendly
- Sulfonylureas
- Glinides
- Thiazolidinediones
- Insulin

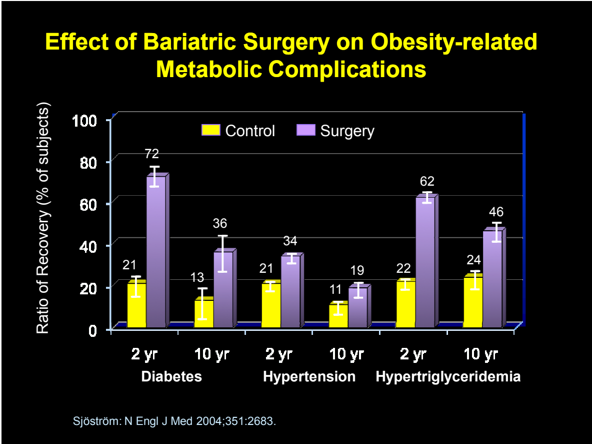
Weight Friendly
- Metformin
- GLP-1 receptor agonists
- DPP-IV Inhibitors
- Pramlintide
- Alpha glucosidase inhibitors
- Colesevalam


WHY WAIT: Weight Loss over Times
Weight change in lbs from baseline
0
-5
-10
-15
-20
-25
-30
-11.2
-16.97
Program End
(9.8% weight loss)
-23.5
-23
-25.1
-25.43
-25.23
-24.82
-24.5
0 1 2 3 4 5 6 7 8 9
Months of follow-up


Changes in A1c and hsCRP
0 1 2 3 4 5 6 7 8
A1c
CRP
Wk 0
Wk 12

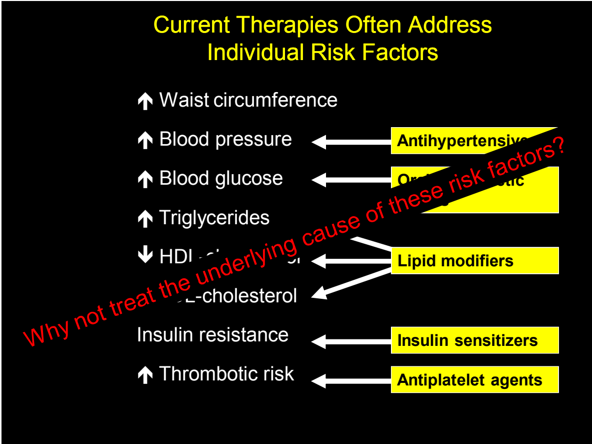

Why WAIT: Traditional RF
0 20 40 60 80 100 120 140
SBP
LDL-C
TG
0
Wk 12





"Overweight and obesity have become to diabetes what tobacco is to lung cancer"

Runge, CF, *Diabetes*, November 2007; 56:2668-272



Weight Loss in Type 2 Diabetes
A Glimpse into the Future

- Moderate weight loss a cornerstone of management
  - Improves glycemic control, reduces BP, improves dyslipidemia
- Achieving weight loss in diabetes
  - Benefit of MNT and diabetes education – yet difficult to sustain
  - Many diabetes therapies associated with weight gain
- Future opportunities for weight management in diabetes
  - Obesity therapies (sibutramine, orlistat, phentermine)
  - Diabetes therapies (GLP-1 agonists, amylin analogs)
  - Surgical interventions (RYGB, Lap Band)

Choosing Antihyperglycemic Agents

- Consider the patient's A1c and glycemic-lowering potential of medications
- Consider nonglycemic actions of medications, such as
  - Cardiovascular risk factors (hypertension, dyslipidemia)
  - Effects that benefit/worsen the prospects of long-term glycemic control
    - Weight gain, insulin resistance, insulin secretory capacity
- Initiating and advancing therapy
  - After diagnosis, determination of additional therapies will depend on several factors that will need to be considered on a per-patient basis
  - The patient is the key player in the diabetes care team
  - The progressive nature of Type 2 diabetes will require the use of combination therapy in most patients over time.

Nathan DM, et al., *Diabetes Care* published online on December 17, 2008 as dc08-9025

Summary

- Weight gain from diabetes medications
  - Worsens cardiovascular risk factors
    - Especially blood pressure
  - Is unacceptable for patients
    - Will not choose therapy known to cause weight gain
    - May discourage patients from taking medications
- Is avoidable with several antihyperglycemic therapies
  - Metformin
  - Sitagliptin
  - Exenatide
  - Pramlintide
- Data from bariatric surgery is promising