Obesity Medicine
Epidemiology & Pathophysiology
Treatment Options – Efficacy & Safety
Benefits of Weight Loss Therapy

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Endocrine University at Mayo Clinic, Rochester, MN
Tuesday, 08 March 2016
OBESITY MEDICINE: BENEFITS OF WEIGHT LOSS THERAPY

Dr. Daniel L. Hurley
Obesity Management
Benefits of Weight Loss Therapy

• **Objectives** – to review:
  • Weight loss outcomes of obesity-related complications
    ▪ Pre-diabetes
    ▪ Type 2 Diabetes
    ▪ CVD risk factors
    ▪ Mechanical-related complications (OSA, OA, GERD, etc.)
Modest (5-10%) Weight Loss Improves T2DM Outcomes

- Improved metabolic control
- Reduced use of medication
- Improved comorbidities
- Decrease mortality

Effect of Dietary Patterns on CVD Risk Factors in RCTs

- SBP, mm Hg
- DBP, mm Hg
- LDL-C, mg/dl
- HDL-C, mg/dl
- Triglycerides, mg/dl
- Glucose, mg/dl
- Insulin, mcU/ml
- CRP, mg/dl

Graph showing unit change for different dietary patterns:
- DASH low fat
- DASH high protein
- DASH high MUFA
- Mediterranean diet
Small Amounts of Wt Gain or Loss Have Important Effects on CHD Risk

Framingham Offspring Study 16-year Follow-up*

*Patients with Low HDL-C, high cholesterol, high BMI, high SBP, high TG, high FBG.

**P <0.002 vs baseline. CHD, coronary heart disease.

OBESITY Medicine: Benefits of Weight Loss Therapy

THERAPEUTIC BEHAVIOR LIFESTYLE CHANGE
Approach to Overweight & Obesity

Weight loss goals

• **The goal** for patients overweight or obese is to **lose 5 to 10%** of current body weight over the ensuing 6 to 12 months

• **Combined therapy** is considered the most successful intervention for weight loss and weight maintenance

Patients Often Have Unrealistic Goals for Weight Loss

<table>
<thead>
<tr>
<th>Weight (lb)</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial weight</strong></td>
<td>218</td>
</tr>
<tr>
<td>Disappointed weight</td>
<td>180</td>
</tr>
<tr>
<td>Acceptable weight</td>
<td>163</td>
</tr>
<tr>
<td>Happy weight</td>
<td>150</td>
</tr>
<tr>
<td><strong>Goal weight</strong></td>
<td>146</td>
</tr>
<tr>
<td>Dream weight</td>
<td>135</td>
</tr>
</tbody>
</table>

60 women, BMI 36.3, 16 kg average wt loss over 48 wks

“Don’t step on it... it makes you cry.”
Energy Homeostasis

Body Weight

Increase
- Energy intake
  - Ingestion of:
    - Proteins
    - Fats
    - Carbohydrates
- Genetics
- Environment
- Behavior

Decrease
- Energy expenditure
  - Physical activity
  - Meal-induced thermogenesis
  - Basal metabolic rate
- Genetics
- Environment
- Behavior
## Measuring Metabolic Rate

**Clinical validity to set realistic expectations**

<table>
<thead>
<tr>
<th>Procedure Time: 09:00</th>
<th>Date: 20-Mar-2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 39</td>
<td>Gender: Female</td>
</tr>
</tbody>
</table>

| **Respiratory Energy Expenditure (REE)** | **INDIRECT CALORIMETRY ASSESSMENT** |

<table>
<thead>
<tr>
<th>Measured Value</th>
<th>Predicted</th>
<th>% Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}O_2$ (ml/min)</td>
<td>163</td>
<td></td>
</tr>
<tr>
<td>Respiratory Quotient (RQ)</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>REE (kcal/24 hours)</td>
<td>1115</td>
<td>1363</td>
</tr>
<tr>
<td>Temp (C)</td>
<td>36.5</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>O$_2$ Saturation (SpO$_2$)</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

### Comments:
- Steady state achieved.
- Usual AM medication taken.
# Measuring Metabolic Rate

Clinical validity to set realistic expectations

## Resting Energy Expenditure (REE)
**INDIRECT CALORIMETRY ASSESSMENT**

<table>
<thead>
<tr>
<th>Procedure Time: 10:00</th>
<th>Date: 21-Mar-2014</th>
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</thead>
<tbody>
<tr>
<td>Age: 77</td>
<td>Gender: Female</td>
</tr>
<tr>
<td>Height: 171 cm</td>
<td>Wt: 116.5 kg</td>
</tr>
<tr>
<td>BMI: 39.84</td>
<td>BSA: 2.25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Measured</th>
<th>Predicted</th>
<th>%Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\dot{V}O_2$ (ml/min)</td>
<td>217</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Quotient (RQ)</td>
<td>0.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REE (kcal/24 hours)</td>
<td>1484</td>
<td>1714</td>
<td>87</td>
</tr>
<tr>
<td>Temp (C)</td>
<td>36.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O$_2$ Saturation (SpO$_2$)</td>
<td>94</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comments:**
Steady state achieved.
**Interventions:**

- In-person center-based or telephone-based one-to-one weight loss counseling, available over a 2-year period.
- Behavioral goals were an energy-reduced, nutritionally adequate diet, facilitated by the inclusion of prepackaged food items in a planned menu during the initial weight loss phase.
- Increased physical activity.

**Usual Care:**

- Participants received 2 individualized weight loss counseling sessions and monthly contacts.

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Rock et al. JAMA 2010;304:1803-1810.
Look AHEAD Study
1-Year Weight Loss Success Factors*

*5,145 M&F with T2DM; Randomized to Intensive Lifestyle Intervention (ILI) or Control.

Long-term Limitations of Weight Loss Benefits in T2DM

Look AHEAD Trial (N=5145)

Estimated mean weight (kg)

Main effect: -4 (95% CI -5 to -3)
P<0.001

Estimated mean A1C (%)

Main effect: -0.22 (95% CI -0.28 to -0.16)
P<0.001

*P<0.05 for between-group comparison. Main effect is the average of post-baseline differences.

CI, confidence interval; T2DM, type 2 diabetes mellitus.
Effects of ILI on CVD in T2DM

Look AHEAD Trial

Patients experiencing death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for angina (%)

Hazard ratio, 0.95 (95% CI, 0.80–1.09) P=0.51

No. at Risk
Control 2575 2425 2296 2156 2019 2049 688
Intervention 2570 2447 2326 2192 2049 505

Effect of Weight Loss in T2DM on CV Risk Factors

Look AHEAD Trial (N=5145)

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>4 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DSE</td>
<td>ILI</td>
</tr>
<tr>
<td>Weight loss (%)</td>
<td>-0.7</td>
<td>-8.6</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>-0.14</td>
<td>-0.64*</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>-7.2</td>
<td>-21.5*</td>
</tr>
<tr>
<td>% on T2DM drugs</td>
<td>2.2</td>
<td>-7.8*</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>-2.8</td>
<td>-6.8*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>-1.8</td>
<td>-3.0*</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>-5.7</td>
<td>-5.2</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>1.4</td>
<td>3.4*</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>-14.6</td>
<td>-30.3*</td>
</tr>
</tbody>
</table>

*P≤0.001, †P=0.01 vs customary support. BP, blood pressure; CV, cardiovascular; DSE, diabetes support and education; ILI, intensive lifestyle intervention; T2DM, type 2 diabetes mellitus.

OBESITY Medicine: Benefits of Weight Loss Therapy

THERAPEUTIC BEHAVIOR LIFESTYLE CHANGE + DRUG THERAPY
Intensive Lifestyle Intervention Prevents Progression From IGT to T2DM

Diabetes Prevention Program (DPP) (n=3234)

Diabetes Incidence per 100 Person-Years

- Intensive lifestyle intervention* (n=1079): 4.8
- Metformin 850mg BID (n=1073): 7.8
- Placebo (n=1082): 11

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat meal plan and ≥150 min/week moderate intensity physical activity.

IGT, impaired glucose tolerance; T2DM, type 2 diabetes mellitus.

DPP Trial

- 3234 individuals at risk for T2DM
  - IFG at baseline
- Randomized to:
  a) Placebo
  b) Metformin
  c) Lifestyle
- Increased activity (150 min/week)
- Improved eating habits
- Mean follow-up of 2.8 years

Intensive Lifestyle Intervention Prevents T2DM as Populations Age

Diabetes Prevention Program (DPP) (n=3234)

Diabetes Incidence per 100 Person-Years

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-44</td>
<td>11.6</td>
<td>6.7</td>
<td>6.2</td>
</tr>
<tr>
<td>45-59</td>
<td>10.8</td>
<td>7.6</td>
<td>4.7</td>
</tr>
<tr>
<td>≥60</td>
<td>10.8</td>
<td>9.6</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat meal plan and ≥150 min/week moderate intensity physical activity

Effect of Lifestyle Intervention

T2DM Prevention Wanes as Weight Increases

Diabetes Prevention Program (DPP) (n=3234)

Diabetes Incidence per 100 Person-Years

BMI (kg/m²)

<table>
<thead>
<tr>
<th>BMI Range</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Lifestyle</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 to &lt;30</td>
<td>9</td>
<td>8.8</td>
<td>3.3</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>8.9</td>
<td>7.6</td>
<td>3.7</td>
</tr>
<tr>
<td>≥35</td>
<td>14.3</td>
<td>7.0</td>
<td>7.3</td>
</tr>
</tbody>
</table>

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat meal plan and ≥150 min/week moderate intensity physical activity

Lifestyle Intervention + Orlistat

XENDOS STUDY: Effect on Weight Loss

4-year double-blind study of 3305 patients, BMI ≥30
5.8 kg ↓ with Orlistat vs 3.0 kg ↓ with placebo (P<0.001)

Lifestyle Intervention + Orlistat

XENDOS Study: Prevention of T2DM

- 3305 patients, BMI ≥30, 79% with NGT and 21% with IGT

NGT = normal glucose tolerance; IGT = impaired glucose tolerance.

Phentermine/topiramate-ER
SEQUEL: 2-year effect on blood pressure and medication use

Phentermine/topiramate-ER
SEQUEL 2-Effect on lipids and medication use

Phentermine/topiramate-ER
SEQUEL 2-Year Effect on HbA1c and medication use

Phentermine/topiramate-ER
Prevention of Progression to T2DM (108 weeks)

PCDB-RCT of 475 subjects with overweight/obesity and 2 or more CV risk factors, and meeting criteria for pre-DM or Metabolic Syndrome. Significant decline in progression to T2DM with 5-10% weight loss.
Lorcaserin – BLOOM Trial
Overweight/obesity Management

# Lorcaserin – BLOOM Trial

## Effect on Cardio-metabolic Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Lorcaserin 10 mg (5.8%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓ -1.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓ -1.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -6.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, %</td>
<td>↓ -0.90</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↑ 2.87</td>
<td>0.049</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -1.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>↓ -21.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Lorcaserin – BLOOM DM Trial
Effect on Glucose in T2DM

- 1-year, RCT, 604 patients 1:1:1 to placebo, or lorcaserin 10 mg q.d. or b.i.d.
- Patients at baseline were treated with metformin, a sulfonylurea or both.
- Baseline HbA1c 7-10%; age 18-65 years; BMI 27-45 kg/m²

### Naltrexone/Bupropion-SR COR II Obesity Study

Effect on Cardio-metabolic Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors (Mean % Weight Loss)</th>
<th>Naltrexone/Bupropion SR (6.4%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↑ 0.6</td>
<td>0.039</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↑ 0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, %</td>
<td>↓ -9.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C, %</td>
<td>↓ -6.2</td>
<td>0.008</td>
</tr>
<tr>
<td>HDL-C, %</td>
<td>↑ 3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>↓ -28.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FBG, mg/dL</td>
<td>↓ -2.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

Liraglutide vs Orlistat
Effect on Body Weight Over 2-Years

## Liraglutide vs Orlistat
### Effect on Cardio-metabolic Risk Factors

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Liraglutide* (5.3%)</th>
<th>Orlistat (2.3%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP, mmHg</td>
<td>↓ -4.6</td>
<td>↓ -1.5</td>
<td>0.039</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>↓ -2.0</td>
<td>↓ -1.5</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>↓ -9.7</td>
<td>↑ 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>↓ -1.0</td>
<td>↓ -13.1</td>
<td>NS</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>↑ 2.3</td>
<td>↓ -0.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Pooled results of liraglutide 2.4 mg and 3.0 mg groups.
BP: blood pressure
COR II: CONTRAVE Obesity Research II
FBG: fasting blood glucose
SR: sustained release

OBESITY Medicine: Benefits of Weight Loss Therapy

BARIATRIC SURGERY
Bariatric Surgery Outcomes

1-Year Effect on Weight-related Comorbidity

ACS Bariatric Surgery Center Network Prospective Observational Study (n=28,616)

*Small numbers of patients with 1 year of follow-up for all comorbidities (n≤38).

†P<0.05 vs LAGB; ‡P<0.05 vs LRYGB.

ACS, American College of Surgeons; BMI, body mass index; GERD, gastroesophageal reflux disease; LAGB, laparoscopic adjustable gastric band; LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass.

Bariatric Surgery Outcomes
Patients With Type 2 Diabetes

- Intensive medical therapy
- Sleeve gastrectomy
- Roux-en-Y gastric bypass

Δ A1C (%)

Δ FPG (mg/dL)

Baseline 3 6 9 12

P<0.001

Intensive Medical Rx

LSG

RYGP

P=0.02

P<0.001

Average no. diabetes medications

Δ BMI (kg/m²)

Baseline 3 6 9 12

P<0.001

Intensive Medical Rx

LSG

RYGP

P<0.001

Δ A1C (%)

Δ FPG (mg/dL)

Baseline 3 6 9 12

P<0.001

Intensive Medical Rx

LSG

RYGP

P=0.02

P<0.001

Average no. diabetes medications

Δ BMI (kg/m²)

Baseline 3 6 9 12

P<0.001

Intensive Medical Rx

LSG

RYGP

P<0.001

Bariatric Surgery Outcomes
Mortality Reduced in Severely Obese Patients

Swedish Obese Subjects Study (n=4047)

Fatal CV Events

<table>
<thead>
<tr>
<th>Years</th>
<th>Control (49 events)</th>
<th>Surgery (28 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>6</td>
<td>0.010</td>
<td>0.010</td>
</tr>
<tr>
<td>12</td>
<td>0.015</td>
<td>0.015</td>
</tr>
<tr>
<td>18</td>
<td>0.020</td>
<td>0.020</td>
</tr>
</tbody>
</table>

HR, 0.56; 95% CI, 0.35-0.88; Log-rank P = 0.01

Total CV Events

<table>
<thead>
<tr>
<th>Years</th>
<th>Control (49 events)</th>
<th>Surgery (28 events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>6</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>12</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>18</td>
<td>0.08</td>
<td>0.08</td>
</tr>
</tbody>
</table>

HR, 0.83; 95% CI, 0.69-1.00; Log-rank P = 0.05

No. at risk

<table>
<thead>
<tr>
<th>Control</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2037</td>
<td>2010</td>
</tr>
<tr>
<td>1993</td>
<td>1970</td>
</tr>
<tr>
<td>1423</td>
<td>1557</td>
</tr>
<tr>
<td>405</td>
<td>412</td>
</tr>
<tr>
<td>2037</td>
<td>2010</td>
</tr>
<tr>
<td>1945</td>
<td>1921</td>
</tr>
<tr>
<td>1326</td>
<td>1468</td>
</tr>
<tr>
<td>361</td>
<td>375</td>
</tr>
</tbody>
</table>

BMI entry criteria: ≥34 kg/m² men, ≥38 kg/m² women.
<table>
<thead>
<tr>
<th>OBESITY COMPILATION</th>
<th>% weight loss required for therapeutic benefit</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2DM Prevention</td>
<td>3% to 10%</td>
<td>Maximum benefit 10%</td>
<td>DPP (Lancet, 2009) SEQUEL (Garvey et al, 2013)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5% to &gt;15%</td>
<td>BP still decreasing &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>Dyslipidemia (TG/HDL)</td>
<td>3% to &gt;15%</td>
<td>TG still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>T2DM (A1c)</td>
<td>3% to &gt;15%</td>
<td>HbA1c still decreasing at &gt;15%</td>
<td>Look AHEAD (Wing, 2011)</td>
</tr>
<tr>
<td>NAFLD</td>
<td>10%</td>
<td>Improves steatosis, inflammation, mild fibrosis</td>
<td>Assy et al, 2007; Dixon et al, 2004; Anish et al, 2009</td>
</tr>
<tr>
<td>Sleep Apnea (AHI)</td>
<td>10%</td>
<td>Little benefit at ≤ 5%</td>
<td>Sleep AHEAD (Foster, 2009) Winslow et al, 2012</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5-10%</td>
<td>Improves symptoms and joint stress mechanics</td>
<td>Christensen et al, 2007 Felson et al, 1992; Aaboe et al, 2011</td>
</tr>
<tr>
<td>Stress Incontinence</td>
<td>5-10%</td>
<td></td>
<td>Burgio et al, 2007 Leslee et al, 2009</td>
</tr>
<tr>
<td>GERD</td>
<td>5-10% women 10% men</td>
<td></td>
<td>Singh et al, 2013 Tutujian R, 2011</td>
</tr>
</tbody>
</table>

SUMMARY: Obesity Medicine

• **Lifestyle intervention** effectively prevents T2DM and improves CVD risk outcomes
  • Lifestyle alone is less effective in more obese populations

• **Weight loss** with lifestyle change is difficult to maintain long-term
  • Ongoing behavioral support from healthcare teams and/or structured support groups can help maintain weight loss

• **Pharmacotherapy** is more effective when combined with lifestyle changes

• **Healthcare professionals** should encourage realistic goals (5-10% initial weight loss), support groups, and adherence to weight loss/maintenance behaviors
Thank You

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