“A Heavy Burden: Obesity and Diabetes”

Diabetes In and Out
University of Rochester School of Medicine and Dentistry
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Duality of Interests

- **Consultant/Advisory Boards**
  - ISIS Pharmaceuticals
  - Merck
  - Novo Nordisk
  - Regeneron/Sanofi

- **Grants/Research Fellowships**
  - ISIS Pharmaceuticals
  - UniQure

- **Medical Education**
  - CMHC
  - Medscape
  - Medical Education Resources
  - MedIntelligence
  - VOX Media
Objectives

• Discuss the etiologies of obesity and the science behind the defense of body weight (fat).

• Review the therapeutic options for treating obesity in patients with type 2 diabetes.
Pathogenic Factors in Obesity

Genes
- Monogenic
- Polygenetic

Environment
- Food availability
- Diet composition
- Physical activity
- Drugs

Pathway Adjustment
- Development
- Postnatal factors
- Epigenetic

Psychology
- Behavior patterns
- Depression
- Culture
Genetic Determinants of “T2DM” and Obesity

- Rare Monogenic (<1%)
- MODY (1-5%)
- Common Gene Variants

T2DM: 15%

- Additional variants with smaller effects?
- Less frequent variants with larger effects?
- Untranscribed DNA?
- Micro RNAs?
- Gene-gene interactions?
- Gene-environment interactions?
- Epigenetic effects?

Obesity: 5%
Gene x dietary pattern interactions in obesity: analysis of up to 68,317 adults of European ancestry

Jennifer A. Nettleton¹, Jack L. Follis², Julius S. Ngwa³, Caren E. Smith⁴,⁵, Shafqat Ahmad⁶, Toshiko Tanaka⁸, Mary K. Wojczynski⁹, Trudy Voortman¹⁰,¹¹, Rozenn N. Lemaitre¹², Kati Kristiansson¹³, Marja-Liisa Nuotio¹³,¹⁵, Denise K. Houston¹⁶, Mia-Maria Perälä¹⁴, Qibin Qi¹⁸,¹⁹, Emily Sonestedt⁷, Ani Manichaikul²⁰,²¹, Stavroula Kanoni²², Andrea Ganna²³, Vera Mikkilä²⁴,²⁷, Kari E. North²⁸, David S. Siscovick²⁹, Kennet Harald³⁰, Nicola M. Mckeown⁴,⁵, Ingegerd Johansson³¹, Harri Rissanen³⁰, Yongmei Liu¹⁷, Jari Lahti²⁵,³⁵, Frank B. Hu¹⁸, Stefania Bandinelli³⁶, Gull Rukh⁷, Stephen Rich²⁰,
Prevention of Weight Gain

• It’s all a matter of energy balance!
  – In the absence of edematous disorders, if you’re burning less than you’re eating you gain weight

\[ E_{\text{Out}} < E_{\text{In}} \]
Obesity Incidence Based on Energy Balance Calculations

- BMI – 25.0 kg/m², Ht - 68”, Wt – 164 lb vs.
- BMI – 30.0 kg/m², Ht – 68”, Wt – 197 lb over 25 years is 10 kcal/day excess
Body Weight Regulation

SET OR SETTLING POINT?
Schematic Representation of the Natural History of Obesity

Multiple Hormonal Signals Influence Food Intake

- Leptin
- Adiponectin
- GLP-1
- Ghrelin
- PYY
- CCK
- Amylin
- Insulin

Organ:
- Adipose Tissue
- Gut
- Pancreas

Hormonal signals
Once obesity occurs, body fat is defended!
Long-Term Follow-Up of Behavioral Treatment for Obesity

Preservation of Weight Loss by Different Interventions

Svetkey LP et al, JAMA 299:1139, 2008
The Biology of Reduced Obesity

- ↓ leptin, ↑ ghrelin, ↓ GLP-1
  - ↑ appetite
  - ↑ preference for energy dense foods
- ↑ insulin sensitivity
  - ↓ adipose tissue TG lipolysis
  - ↓ pro-inflammatory cytokines
  - ↑ adipose tissue lipoprotein lipase
  - ↓ skeletal muscle lipoprotein lipase
  - ↑ CHO oxidation & ↑ fat storage
- ↓ physical activity

How much change in AT mass is needed to be defended?

Let’s ask this question in walking-well normal weight women.
Total Body % Fat Changes: DXA

Control

Lipectomy

Change from Baseline (%)

6 wk

12 mo
Change in Trunk Fat (DEXA) in Normal Weight Women after Suction Lipectomy

So even in walking-well normal weight women, total body fat is defended one year after suction lipectomy - and perhaps in less favorable locations!

Brain cells come and brain cells go, but fat cells live forever.
Predictors of Weight Loss Maintenance: NWCR

- **Energy Intake**
  - avoid frying
  - substitute low-fat for high-fat

- **Leisure Time Exercise**
  - # of strenuous activities/wk
  - # of sweat episodes/wk

- **Restraint Scale**
  - Concern about dieting
  - Weight fluctuation

Pharmacotherapy for Reduced-Obesity Maintenance

• Appetite typically increases after successful weight reduction, a predictor or weight regain.
• All pharmacological agents except orlistat used in obesity treatment work by reducing appetite and decreasing food intake.
• Anti-obesity drugs have been associated with improved weight-loss maintenance after 12 kg of weight reduction.
  – Johansson K et al, AJCN, 99:14, 2014
Weight Loss Maintenance in 20 Randomized Controlled Trials

Johansson K et al, AJCN, 99:14, 2014
Progression to Type 2 Diabetes

At the time of diagnosis, ~50% of insulin secretory capacity has been lost.

Prandial defect occurs first.

From normal

Insulin Secretion
Insulin Resistance
Postprandial Glucose
Fasting Glucose

Years From Diagnosis

Approaches to Weight Loss in Patients with Type 2 Diabetes
## Weight Effects of Glucose-Lowering Medications

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Weight effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 analogs</td>
<td>↓</td>
</tr>
<tr>
<td>Metformin</td>
<td>± or ↓</td>
</tr>
<tr>
<td>Bromocryptine</td>
<td>↓</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>↓</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>±</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>±</td>
</tr>
<tr>
<td>Insulin</td>
<td>↑</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>↑</td>
</tr>
<tr>
<td>Glinides</td>
<td>↑</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>↑</td>
</tr>
</tbody>
</table>

Eckel RH et al. *Diabetes Care* 34:1424-1430; 2011
Approaches to Weight Loss in Patients with Type 2 Diabetes

- Lifestyle
- Behavioral modification
- Medications
- Metabolic surgery
Weight Loss in T2DM and Less CVD: Did *Look AHEAD* Answer All the Questions?

- **Primary Objective** – To assess the long-term (11.5 yr) effects of an intensive weight loss program over 4 years in overweight and obese subjects with type 2 diabetes.
  - n = 5145 men and women in 16 study centers
  - Weight loss vs. support and education
  - age: 45-74 yr
  - BMI > 25 kg/m2
  - Primary outcome – time to a major CVD event
  - Secondary outcomes – many
  - Study stopped early for no benefit on primary outcome

Look AHEAD: Weight Change

![Graph showing weight change over years for intervention and control groups. The graph indicates a main effect of intervention with a 95% CI of -5 to -3 and a p-value less than 0.001.]
Look AHEAD: Glycated Hb Change

D Glycated Hemoglobin

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

Year

Intervention
Control

Look AHEAD Study Group, NEJM 369:145, 2013
Look AHEAD: Change in BP

**SBP**

Main effect: $-1.9 (-2.6, -1.1), p<0.05$

**DBP**

Main effect: $-0.1 (-0.5, 0.3), p=0.72$

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Look AHEAD: Change in HDL-C

Main effect: 1.2 (0.6, 1.9), p<0.05

Intervention
Control

Look AHEAD: Change in LDL-C


![Graph showing change in LDL-C levels over years with intervention and control groups compared.](image-url)
Look AHEAD: Change in Rx

Insulin, Statin and Antihypertensive Use

- Antihypertensive
- Statin
- Insulin

Year

Intervention
Control

Look AHEAD Study Group, NEJM 369:145, 2013
Look AHEAD: Primary MACE Outcome

The Look AHEAD Trial: A Review and Discussion Of Its Outcomes

Xavier Pi-Sunyer, MD, MPH
Columbia University College of Physicians and Surgeons, P&S PO Box 30 DOM/NYORC, 630 West 168th Street, New York, NY 10032, Phone: 212 523 4161, Fax: 212 523 4830, fxp1@columbia.edu

Abstract

The LookAhead trial was a randomized controlled trial comparing an Intensive Lifestyle Intervention (ILI) to a Diabetes Support and Education (DSE) in overweight and obese type 2 diabetes patients to track the development of cardiovascular disease over time. The trial intervention was stopped for futility after a median follow-up of 9.6 years. While there was a differential effect on weight loss and fitness between the two groups, there was no effect on cardiovascular outcomes. Cardiovascular events were less than half the projected rate per year in the DSE group; thus there was a very low over-all rate of events in both groups. There were many other health benefits of ILI, including improved biomarkers of glucose and lipid control, less sleep apnea, lower liver fat, less depression, improved insulin sensitivity, less urinary incontinence, less kidney disease, reduced need of diabetes medications, maintenance of physical mobility, improved quality of life and lower costs.
Why Did Look AHEAD Fail?

- Insufficient power?
  - In particular subgroups
    - No CVD history?
- More weight loss and maintenance was needed?
  - But what about dietary composition (<30% fat)?
- Educational sessions in Control group?
- Statin drop-in in the Control group?
- Patients in both groups were reasonably well managed for CVD risk?
Greater Weight Loss Further Reduces the Incidence of New-Onset Diabetes

Diabetes Prevention Program

Incidence rate per 100 person-years

Change in weight from baseline (kg)

Genetic Risk vs. Lifestyle in T2DM? (TCF7L2 SNP)

Lifestyle intervention “trumps” genetic risk

The New Options

• FDA approved drugs within the last 4 years
  – Phentermine/Topiramate ER
  – Lorcaserin
  – Naltrexone/bupropion
  – Liraglutide
Neuron Populations in the ARC

Two neuron populations with opposing effects on food intake in the hypothalamic arcuate nucleus (ARC):

Stimulate food intake
- NPY (neuropeptide Y)
- AgRP (agouti-related peptide)

Suppress food intake
- POMC (proopiomelanocortin)
- CART (cocaine- and amphetamine-regulated transcript)
Phentermine/Topiramate ER
Mechanism of Action

- Phentermine
  - Sympathomimetic amine - NE release
Phentermine Increases Norepinephrine Release

Effects of NE Drugs

Tyrosine → Tryptophan hydroxylase → DOPA → NE

Phentermine

???

Mazindol → Slows firing

Clenbuterol

???
Phentermine/Topiramide ER: Mechanism of Action

- Phentermine
  - Sympathomimetic amine - NE release
- Topiramide
  - ↑ GABA activity
  - ↓ AMPA/kainate glutamate receptor
  - ↓ carbonic anhydrase
Topiramate Action on GABAergic Neurons
Phentermine/Topiramate ER Prevents Progression to T2DM: SEQUEL


Annualized Incidence of T2DM

- Placebo: 3.7%
- Phen/TPM ER 7.5/46 mg: 1.7% (P = 0.15)
- Phen/TPM ER 15/92 mg: 0.9% (P < 0.01)

Effects of Phentermine/Topiramate ER in Patients with T2DM: SEQUEL


\[ P = 0.013 \] for between-group differences.

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in A1C</th>
<th>Placebo (n=55)</th>
<th>Phen/TPM ER 7.5/46 mg (n=26)</th>
<th>Phen/TPM ER 15/92 mg (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-0.04</td>
<td>6.9</td>
<td>7.3</td>
<td>6.9</td>
</tr>
<tr>
<td>Phen/TPM ER 7.5/46 mg</td>
<td>-0.42</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phen/TPM ER 15/92 mg</td>
<td>-0.23</td>
<td></td>
<td></td>
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</table>

Patients With Net Change* in Diabetes Medications (%)

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<thead>
<tr>
<th>Group</th>
<th>Patients With Net Change* in Diabetes Medications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=227)</td>
<td>7.1</td>
</tr>
<tr>
<td>Phen/TPM ER 7.5/46 mg</td>
<td>1.9</td>
</tr>
<tr>
<td>Phen/TPM ER 15/92 mg</td>
<td>0</td>
</tr>
</tbody>
</table>
Lorcaserin: Mechanism of Action

• Selective $5\text{-HT}_{2C}$ receptor agonist
  – $\uparrow$ POMC
• $\uparrow$ $\alpha$-MSH
  – $\downarrow$ food intake
Lorcaserin Dose in Obese Patients with Type 2 Diabetes Mellitus: BLOOM-DM

- Lorcaserin 10 mg BID
- Lorcaserin 10 mg QD
- Placebo

Proportion of patients who lost ≥5% or ≥10% of body weight from baseline to week 52: Completers

Lorcaserin, Change in Glycemic Parameters: BLOOM-DM

**A1C**

-5.0 \(-2.5 \) \(-1.0 \) \(-0.5 \) 0 12 24 36 52

**Fasting plasma glucose**

-40 \(-30 \) \(-20 \) \(-10 \) 0 12 24 52

Study week

Lorcaserin 10 mg BID  Lorcaserin 10 mg QD  Placebo

50% Lorcaserin and 26% on placebo achieved A1C < 7.0%

*P <0.001; **P <0.05

### Newest FDA-Approved Weight Loss Drugs

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion/Naltrexone</td>
<td>• Dopamine/NE reuptake inhibitor&lt;br&gt;• Opioid receptor antagonist</td>
<td>• June, 2014</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>• GLP-1 receptor agonist</td>
<td>• Dec, 2014</td>
</tr>
</tbody>
</table>
Weight Loss in Patients with T2DM with Naltrexone-Bupropion

Hollander P et al, Diabetes Care 36:422, 2013
Effect of Naltrexone-Bupropion on Hb A1c in Patients with T2DM

GLP-1 Effects in Humans: Understanding the Metabolic Role of Incretins

GLP-1 secreted upon the ingestion of food

Beta cells:
- Enhances glucose-dependent insulin secretion

Alpha cells:
- Postprandial glucagon secretion

Liver:
- Glucagon reduces hepatic glucose output

Stomach:
- Helps regulate gastric emptying

Promotes satiety and reduces appetite

Beta-cell workload
Liraglutide Approved for Diabetes Also Reduces Body Weight

Matching Medication to Patient

When NOT TO USE:

Lorcaserin
  – Patient on a lot of SSRI and/or SNRI

Orlistat
  – GI disorders

Phentermine/topiramate
  – Pregnant-age women not on birth control
  – Uncontrolled HTN
  – Uncontrolled or active CVD

Naltrexone/bupropion
  – Suicidal ideation
  – Uncontrolled HTN

Liraglutide
  – MCT at risk patients
Greater Hunger and Less Restraint Predict Weight Loss Success With Phentermine Treatment

Elizabeth A. Thomas¹⁄², Bryan McNair³, Jamie L. Bechtell¹⁄², Annie Ferland¹, Marc-Andre Cornier¹⁄², and Robert H. Eckel¹

Objective: Phentermine is thought to cause weight loss through a reduction in hunger. It was hypothesized that higher hunger ratings would predict greater weight loss with phentermine.

Methods: This is an observational pilot study in which all subjects were treated with phentermine for 8 weeks and appetite and eating behaviors were measured at baseline and week 8. Outcomes were compared in subjects with ≥5% vs. <5% weight loss, and linear regression was used to identify predictors of percent weight loss.

Results: Twenty-seven subjects (37 ± 4.5 years, 93.8 ± 12.1 kg, BMI 33.8 ± 3.1 kg m⁻²) completed the study, with mean weight loss of −5.4 ± 3.3 kg (−5.7% ± 3.2%). Subjects with ≥5% weight loss had higher baseline pre-breakfast hunger (P = 0.017), desire to eat (P = 0.003), and prospective food consumption (0.006) and lower baseline cognitive restraint (P = 0.01). In addition, higher baseline home prospective food consumption (P = 0.002) and lower baseline cognitive restraint (P < 0.001) were found to be predictors of weight loss.
Empagliflozin (EMPA-REG)

Adapted from Inzucchi SE et al. *Diab Vasc Dis Res* 12:90, 2015
Bariatric-metabolic surgery versus conventional medical treatment in obese patients with type 2 diabetes: 5 year follow-up of an open-label, single-centre, randomised controlled trial

Geltrude Mingrone, Simona Panunzi, Andrea De Gaetano, Caterina Guidone, Armerigo Iaconelli, Giuseppe Nanni, Marco Castagneto, Stefan Bornstein, Francesco Rubino

Summary

Background Randomised controlled trials have shown that bariatric surgery is more effective than conventional treatment for the short-term control of type-2 diabetes. However, published studies are characterised by a relatively short follow-up. We aimed to assess 5 year outcomes from our randomised trial designed to compare surgery with conventional medical treatment for the treatment of type 2 diabetes in obese patients.

Methods We did our open-label, randomised controlled trial at one diabetes centre in Italy. Patients aged 30–60 years...
Bariatric-metabolic Surgery vs. Medical Treatment in Obese Patients with T2DM: 5 Year Follow-up

• Primary Objective – to assess 5 year outcomes from a randomized trial designed to compare surgery with conventional medical treatment for the treatment of T2DM in obese patients.
  – n = 60 obese patients with T2DM
    • Age 30-60 years; BMI ≥ 35.0 kg/m²; A1c ≥ 7.0%
    • ≥ 5 years duration of T2DM
    • 20 each assigned to
      – Medical treatment
      – Roux-en-Y gastric bypass
      – Biliopancreatic diversion
      88% 5 year follow-up
  – Primary endpoint: A1c of ≤ 6.5% and FPG ≤ 5.6 mmol/L

Bariatric-metabolic Surgery vs. Medical Treatment in Obese Patients with T2DM: Weight

Bariatric-metabolic Surgery vs. Medical Treatment in Obese Patients with T2DM: Remission Rate

Bariatric-metabolic Surgery vs. Medical Treatment in Obese Patients with T2DM: Metabolic Improvement

Bariatric-metabolic Surgery vs. Medical Treatment in Obese Patients with T2DM: CVD Risk

Bariatric-metabolic Surgery vs. Medical Treatment in Obese Patients with T2DM: Cardiovascular Drugs

Bariatric-metabolic Surgery vs. Medical Treatment in Obese Patients with T2DM: HDL Cholesterol

Change in HbA1c: Meta-Analysis of Surgical vs. Medical Trials
Summary and Conclusions

• In obese patients weight loss is difficult to achieve and more difficult to maintain.
  – There is a strong metabolic basis for this.
  – However, success can be achieved.

• In patients with T2DM
  – Lifestyle has many benefits but not CVD event reduction
  – Weight loss medications are effective but must be maintained and CVD benefits remain unproven
  – Bariatric-metabolic surgery appears most effective in reducing A1c, but CVD?
Thank You!