THE OBESITY CONUNDRUM

Practical Approaches for Patients Who Are Obese and “Well”, Obese with Risk Factors, and Obese and “Sick”

THURSDAY, NOVEMBER 14, 2013

COURSE CHAIR
Ken Fujioka, MD

This continuing medical education activity is sponsored by VINDICO medical education.
This activity is supported by an educational grant from Novo Nordisk.
Held in conjunction with ObesityWeek 2013.
THE OBESITY CONUNDRUM

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WELCOME
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[Logo of Novo Nordisk]
Correlation Between Gut and Weight in the Obese Patient: How the Human Body Regulates Body Weight in the Obese

Ken Fujioka, MD
Director, Nutrition and Metabolic Research
Division of Diabetes and Endocrinology
Scripps Clinic
San Diego, CA
Patient A: Back Injury

- Was 155 pounds and doing well
  - Exercises regularly
  - Eats a reasonably healthy diet
- Has a back injury
  - Cannot exercise
  - Sleep is disrupted
  - Eating habits change for the worse
  - Stays at home while recovering from back surgery
- Gains 45 pounds
Two Pathways That Direct Obesity

Effectors

Feeding
Gastric emptying
Metabolic rate

Hypothalamus
Second order neurons
Arcuate nucleus

Hindbrain

Nucleus tractus solitarius

Leptin
Insulin
Adiposity Signals

PPY
GLP-1
PP
OXM
Satiety Peptides

Ghrelin
Hunger Signals

Vagal Afferents

Patient A: Back Injury

- 45-year-old man
- Height is 5 feet 9 inches
- Weight went from 155 lbs to 200 lbs
- BMI changed from 23.5 kg/m² to 31 kg/m²

- Is the patient going to go on to diabetes and be metabolically sick?
  - What predicts this?
Obese Healthy

- Not all individuals who gain weight and become obese will go on to have metabolic abnormalities such as diabetes or metabolic syndrome
  - MHO = Metabolically Healthy Obese
  - OMH = Obese Metabolically Healthy
  - Obese well
  - Obese without cardiometabolic risk factors
- Remember this is a minority of obese patients
Pathophysiology

Chronic Nutrition Overload → Increase in Adipocyte Mass

Low Number of Larger Hypertrophic Adipocytes → Inflammatory State ↑ Free Fatty Acids Insulin Resistance

No Inflammation No ↑ Free Fatty Acids No Insulin Resistance

High Number of Small Adipocytes
NHANES 1999-2004

- Evaluated 6 parameters for metabolic disease
  - Blood pressure
  - Triglycerides
  - Fasting glucose
  - C-reactive protein
  - Low HDL-C
  - Insulin resistance
    - Fasting insulin x FBS/22.5

NHANES Study:
31.7% Metabolically Healthy Obese

- Metabolically healthy: 1 or fewer cardiometabolic abnormalities
- Metabolically unhealthy: 2 or more cardiometabolic abnormalities
- 5440 participants 20 years or older
- Excluded if they had known CV disease

- 31.7% of the obese (BMI > 30 kg/m²) were metabolically healthy
  - 71% white, 11% African American, 18% other

Metabolically Healthy but Obese: Phenotype in African Americans

- 126 obese (BMI ≥ 30 kg/m²) with no known CV disease
- Definition of Metabolically Healthy and Obese
  - HDL-C ≥ 40 mg/dL
  - Absence of diabetes (random < 200 mg/dL and fasting < 126 mg/dL)
  - Blood pressure 140/90 mm Hg or better
- 28.5% Metabolically Healthy and Obese
  - Average BMI 44 kg/m² for both Healthy and Unhealthy

Discordant Risk: Overweight and Cardiometabolic Risk in Chinese

- 2009 China Health and Nutrition Survey
- 8,233 adults (age 18 to 98)
- BMI ≥ 23 kg/m² (“Asian cut point”)
  - Prediabetes or diabetes (A1C > 5.7%)
  - High C-reactive protein ≥ 3mg/L
  - Blood pressure ≥ 130/85 mm Hg
  - Triglycerides ≥ 150 mg/dL
  - Low HDL-C < 40 mg/dL for men and < 50 mg/dL for women
- 21.7% were metabolically healthy
  - Could not have any of the above
  - 66.8% of BMI < 23 kg/m² metabolically healthy

Metabolic Obesity and Phenotypic Obesity in Asian Indians

- 2350 Asian Indian adults
- BMI $\geq 25$ kg/m$^2$
- Metabolically healthy was not having metabolic syndrome (any 3 of the following):
  - FBS $\geq 100$ mg/dL
  - Blood pressure $\geq 130/85$ mm Hg
  - Triglycerides $\geq 150$ mg/dL
  - Low HDL-C $< 40$ mg/dL for men and $< 50$ mg/dL for women
  - Waist $\geq 90$ cm for men; $\geq 80$ cm for women
- 13.3% metabolically healthy
  - These patients could have had 1 or 2 of the above

Metabolically Healthy Obese Phenotype in Hispanic Participants (IRAS Family Study)

- 1054 Hispanic adults (38% obese)
- Metabolically Healthy BMI ≥ 30 kg/m²
  - One or fewer cardiometabolic risk factors
  - (BS ≥ 100 mg/dL, BP ≥ 130/85 mm Hg, Low HDL-C (< 40 mg/dL and <50 mg/dL), TG ≥ 150 mg/dL, CRP ≥ 3, HOMA-IR > 5.13
- 19% of the Obese met the criteria of Metabolically Healthy
  - When you looked at the % of lean and fat tissue between MHO and metabolically unhealthy they were the same

Summary

- There is good fat and bad fat
- Large fat cells are not good for metabolic health
- Small fat cells are a good thing for metabolic health
- There is a large variation in how different races will handle weight gain
  - Increase in number of fat cells
  - Some races do not have the ability to expand the fat mass and end up with large hypertrophied adipocytes
Characterizing the Obesity Population

- **Obese and “Well”**: Individuals who carry excess weight, but who do not have any comorbidities or risk factors for comorbid conditions and who do not experience any impairments in their daily feeling or functioning.

- **Obese with Risk Factors**: Individuals who carry excess weight who do not yet have any comorbidities, but who have measurable risk factors for comorbid conditions and/or impairments to their daily feeling or functioning.

- **Obese and “Sick”**: Individuals who carry excess weight and who have one or more obesity-attributable comorbidities and impairments to their daily feeling or functioning.

The Obesity Conundrum

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Held in conjunction with ObesityWeek 2013.
Across the Spectrum: Characterizing the Obesity Population to Help Guide Treatment

Arya M Sharma, MD, PhD, FRCPC
Research Chair for Obesity Research & Management
University of Alberta
Medical Director
Alberta Provincial Obesity Program
Edmonton, AB, Canada
www.drsharma.ca
“Ideal Weight”

Synonymous with “desirable weight”

First introduced in 1943 by the Metropolitan Life Insurance Company (MLIC) standard height-weight tables for men and women
## Metropolitan Life Insurance Company (MLIC) Standard Height-Weight Tables for Women

### HEIGHT AND WEIGHT GOALS

<table>
<thead>
<tr>
<th>Height</th>
<th>Small frame</th>
<th>Medium frame</th>
<th>Large frame</th>
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<td>109-121 lbs</td>
<td>113-131 lbs</td>
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<tr>
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<td>103-113</td>
<td>111-123</td>
<td>120-134</td>
</tr>
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<td>135-148</td>
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<td>155-176</td>
</tr>
<tr>
<td>6’0”</td>
<td>138-151</td>
<td>148-162</td>
<td>158-179</td>
</tr>
</tbody>
</table>

BMI=19.3 kg/m²

BMI=25.6 kg/m²
Anatomical Terms Used to Describe Obesity (Historical)

- Cellular
  - hyperplastic
  - hypertrophic

Anatomical Terms Used to Describe Obesity (Historical)

- Cellular
  - hyperplastic
  - hypertrophic
- Somatotypes
  - ectomorphic
  - mesomorphic
  - endomorphic

Anatomical Terms Used to Describe Obesity (Historical)

- Cellular
  - hyperplastic
  - hypertrophic
- Somatotypes
  - ectomorphic,
  - mesomorphic
  - endomorphic

- Body segment
  - central
  - peripheral

Anatomical Terms Used to Describe Obesity (Historical)

- Cellular
  - hyperplastic
  - hypertrophic
- Somatotypes
  - ectomorphic,
  - mesomorphic
  - endomorphic
- Body segment
  - central
  - peripheral
- Distribution pattern
  - android
  - gynoid

Anatomical Terms Used to Describe Obesity (Historical)

- Cellular
  - hyperplastic
  - hypertrophic
- Somatotypes
  - ectomorphic, mesomorphic, endomorphic
- Body segment
  - central
  - peripheral
- Distribution pattern
  - android
  - gynoid
- Depot
  - visceral
  - subcutaneous
  - ectopic (visceral, subcutaneous, ectopic)

Quetelet Index (1832)

body weight (kg)

height (m)^2

Renamed “Body Mass Index” by Ancel Keys in 1972

Adolphe Quetelet (1796–1874)
BMI and Body Fat

DXA scan of two individuals with the same BMI but markedly different percent body fat

Relationship Between BMI and Percent Body Fat in Men and Women

BMI and Risk of Cardiovascular Mortality

Obesity and the risk of myocardial infarction in 27 000 participants from 52 countries: a case-control study

Salim Yusuf, Steven Hawken, Stephanie Öunpuu, Leonardo Bautista, Maria Grazia Franzosi, Patrick Commerford, Chin C Lang, Zvonko Rumboldt, Churchill L Onen, Liu Lisheng, Supachai Tanomsup, Paul Wong Jr, Fahad Razak, Arya M Sharma, Sonia S Anand, on behalf of the INTERHEART Study Investigators

Summary
Background Obesity is a major risk factor for cardiovascular disease, but the most predictive measure for different ethnic populations is not clear. We aimed to assess whether markers of obesity, especially waist-to-hip ratio, would be stronger indicators of myocardial infarction than body-mass index (BMI), the conventional measure.

Methods We did a standardised case-control study of acute myocardial infarction with 27 098 participants in 52 countries (12 461 cases and 14 637 controls) representing several major ethnic groups. We assessed the relation between BMI, waist and hip circumferences, and waist-to-hip ratio to myocardial infarction overall and for each group.

Findings BMI showed a modest and graded association with myocardial infarction (OR 1.44, 95% CI 1.32–1.57 top quintile vs bottom quintile before adjustment), which was substantially reduced after adjustment for waist-to-hip ratio (1.12, 1.03–1.22), and non-significant after adjustment for other risk factors (0.98, 0.88–1.09). For waist-to-hip ratio, the odds ratios for every successive quintile were significantly greater than that of the previous one (2nd quintile: 1.15, 1.05–1.26; 3rd quintile: 1.39, 1.28–1.52; 4th quintile: 1.90, 1.74–2.07; and 5th quintiles: 2.52, 2.31–2.74 [adjusted for age, sex, region, and smoking]). Waist (adjusted OR 1.77; 1.59–1.97) and hip (0.73; 0.66–0.80) circumferences were both highly significant after adjustment for BMI (p<0.0001 top vs bottom quintile). Waist-to-hip ratio and waist-to-hip ratio of circumferences were both highly significant after adjustment for BMI (p<0.0001 top vs bottom quintile).
It does not matter what your BMI is. Even if your BMI is as low, 23 range, the people who have a high waist-to-hip ratio, have a BMI of 23.

You have got the exact same risk for having a myocardial infarct as the person with a BMI of 30 who has a high waist-to-hip ratio.

A lot of this depends on where the fat is actually located.
The people with the greater waist circumference on average are going to have more visceral fat than those with the lower waist circumference on average.
REVIEW

A proposed clinical staging system for obesity

AM Sharma¹ and RF Kushner²

¹Division of Endocrinology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada and ²Division of General Internal Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Current classifications of obesity based on body mass index, waist circumference and other anthropometric measures, although useful for population studies, have important limitations when applied to individuals in clinical practice. Thus, these measures do not provide information on presence or extent of comorbidities or functional limitations that would guide decision making in individuals. In this paper we review historical and current classification systems for obesity and propose a new simple clinical and functional staging system that allows clinicians to describe the morbidity and functional limitations associated with excess weight. It is anticipated that this system, when used together with the present anthropometric classification, will provide a simple framework to aid decision making in clinical practice.

International Journal of Obesity advance online publication, 3 February 2009; doi:10.1038/ijo.2009.2

Keywords: body mass index; obesity staging; obesity diagnosis; obesity treatment
Using the Edmonton obesity staging system to predict mortality in a population-representative cohort of people with overweight and obesity

Raj S. Padwal MSc MD, Nicholas M. Pajewski PhD, David B. Allison PhD, Arya M. Sharma MD PhD

ABSTRACT

Background: Anthropometric-based classification schemes for excess adiposity do not include direct assessment of obesity-related comorbidity and functional status and thus have limited clinical utility. We examined the ability of the Edmonton obesity staging system, a 5-point ordinal classification system that considers comorbidity and functional status, in predicting mortality in a nationally representative US sample.

Methods: We analyzed data from the National Health and Human Nutrition Examination Surveys (NHANES) III (1988–1994) and the NHANES 1999–2004, with mortality follow-up through to the end of 2006. Adults (age ≥ 20 yr) with overweight or obesity who had been randomized to the morning session at the mobile examination centre were scored according to the Edmonton obesity staging system. We examined the relationship between staging system scores and mortality, and Cox proportional hazards models were adjusted for the presence of the metabolic syndrome or hypertriglyceridemic waist.

Results: Over 75% of the cohort with overweight or obesity were given scores of 1 or 2. Scores of 4 could not be reliably assigned because specific data elements were lacking. Survival curves clearly diverged when stratified by scores of 0–3, but not when stratified by obesity class alone. Within the data from the NHANES 1988–1994, scores of 2 (hazard ratio [HR] 1.57; 95% confidence interval [CI] 1.16 to 2.13) and 3 (HR 2.69; 95% CI 1.98 to 3.67) were associated with increased mortality compared with scores of 0 or 1, even after adjustment for body mass index and the metabolic syndrome. We found similar results after adjusting for hypertriglyceridemic waist (i.e., waist circumference ≥ 90 cm and a triglyceride level ≥ 2 mmol/L for men; the corresponding values for women were ≥ 85 cm and ≥ 1.5 mmol/L), as well as in a cohort eligible for bariatric surgery.

Interpretation: The Edmonton obesity staging system independently predicted increased mortality even after adjustment for contemporary methods of classifying adiposity. The Edmonton obesity staging system may offer improved clinical utility in assessing obesity-related risk and prioritizing treatment.

Competing interests: Raj Padwal and Arya Sharma are supported by an alternative funding plan from the Government of Alberta and the University of Alberta. David Allison has received grants, honoraria, donations, and consulting fees from numerous other commercial and nonprofit entities with interests in obesity. No other competing interests were declared.

This article has been peer reviewed.

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Dr. Raj S. Padwal,
padwal@ualberta.ca
EOSS Predicts Mortality in NHANES III

EOSS Predicts Mortality at Every Level of BMI NHANES III

EOSS Predicts Mortality at Every Level of BMI NHANES III


**EOSS: EDMONTON OBESITY STAGING SYSTEM - Staging Tool**

**STAGE 0**
- **NO** sign of obesity-related risk factors
- **NO** physical symptoms
- **NO** psychological symptoms
- **NO** functional limitations

**Case Example:**
Physically active female with a BMI of 32 kg/m², no risk factors, no physical symptoms, no self-esteem issues, and no functional limitations.

**WHO CLASSIFICATION OF WEIGHT STATUS (BMI kg/m²)**
- Obese Class I: 30 - 34.9
- Obese Class II: 35 - 39.9
- Obese Class III: ≥40

**Stage 0 / Stage 1 Obesity**
Patient *does not meet clinical criteria for admission* at this time. Please refer to primary care for further preventative treatment options.

**STAGE 1**
- **Patient has obesity-related SUBCLINICAL** risk factors (borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc) - OR -
- **MILD** physical symptoms - patient currently not requiring medical treatment for comorbidities (dyspnea on moderate exertion, occasional aches/pains, fatigue, etc.) - OR -
- **MILD** obesity-related psychological symptoms and/or mild impairment of well-being (quality of life not impacted)

**Case Example:**
38 year old female with a BMI of 59.2 kg/m², borderline hypertension, mild lower back pain, and knee pain. Patient does not require any medical intervention.

**STAGE 2**
- **Patient has an ESTABLISHED** obesity-related comorbidities requiring medical intervention (HTN, Type II Diabetes, sleep apnea, PCOS, osteoarthritis, reflux disease) - OR -
- **MODERATE** obesity-related psychological symptoms (depression, eating disorders, anxiety disorder) - OR -
- **MODERATE** functional limitations in daily activities (Quality of life is beginning to be impacted)

**Case Example:**
32 year old male with a BMI of 36 kg/m² who has primary hypertension and obstructive sleep apnea.

**STAGE 3**
- **Patient has significant obesity-related end-organ damage** (myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis) - OR -
- **SIGNIFICANT** obesity-related psychological symptoms (major depression, suicide ideation) - OR -
- **SIGNIFICANT** functional limitations (eg: unable to work or complete routine activities, reduced mobility)
- **SIGNIFICANT** impairment of well-being (quality of life is significantly impacted)

**Case Example:**
49 year old female with a BMI of 67 kg/m² diagnosed with sleep apnea, CV disease, GERD, and suffered from stroke. Patient's mobility is significantly limited due to osteoarthritis and gout.

**STAGE 4**
- **SEVERE** (potential end stage) from obesity related comorbidities - OR -
- **SEVERELY** disabling psychological symptoms - OR -
- **SEVERE** functional limitations

**Case Example:**
45 year old female with a BMI of 54 kg/m² who is in a wheelchair because of disabling arthritis, severe hyperpnea, and anxiety disorder.

Sharma AM & Kushner RF, Int J Obes 2009
Management Recommendations by Obesity Stage

**Stage 0:** Identification of factors contributing to increased body weight. Counseling to prevent further weight gain through lifestyle measures including healthy eating and increased physical activity.

**Stage 1:** Investigation for other (non-weight related) contributors to risk factors. More intense lifestyle interventions, including diet and exercise to prevent further weight gain. Monitoring of risk factors and health status.

**Stage 2:** Initiation of obesity treatments including considerations of all behavioral, pharmacological and surgical treatment options. Close monitoring and management of comorbidities as indicated.

**Stage 3:** More intensive obesity treatment including consideration of all behavioral, pharmacological and surgical treatment options. Aggressive management of comorbidities as indicated.

**Stage 4:** Aggressive obesity management as deemed feasible. Palliative measures including pain management, occupational therapy and psychosocial support.

Obesities are heterogeneous complex disorders of multiple etiologies characterized by excess body fat that threatens or affects socioeconomic, mental or physical health

Sharma 2007
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World Science and Treatment Meet
November 11-16, 2013 • Atlanta, GA
Treatment Options for Obesity: When and How Do They Fit?

Louis J. Aronne, MD, FACP
Professor of Clinical Medicine
Weill Cornell Medical College
Director, Comprehensive Weight Control Program
New York, NY
Our Typical Patient

- BMI 37 kg/m^2
- Multiple diagnoses, several usually unrecognized
  - T2DM and proteinuria
- 7 - 8 medications
- Sleep apnea > 50%
- Stage 3

- Treating obesity is a way to treat multiple comorbidities
- You may want to focus on treating people with comorbid illnesses
### Treatment Guidelines are Based on BMI and Comorbid Conditions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>25–26.9</th>
<th>27–29.9</th>
<th>30–34.9</th>
<th>35–39.9</th>
<th>≥40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diet, physical activity, behavior therapy</strong></td>
<td>Yes with comorbidities</td>
<td>Yes with comorbidities</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight-loss surgery</strong></td>
<td></td>
<td></td>
<td>Lap band with DM</td>
<td>Yes with comorbidities</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Yes alone indicates that the treatment is indicated regardless of the presence or absence of comorbidities. The solid arrow signifies the point at which therapy is initiated.*

Do We Stick to Guidelines for Weight Management?

- Yes, with exceptions: Does not apply to surgery

- Examples
  - Severe documented weight gain referred by a health care provider
  - Hormone sensitive tumors like breast or prostate referred by oncology
  - Comorbidity like sleep apnea or T2DM which may respond to weight loss
Medical Complications of Obesity: Almost Every Organ System is Affected, and May Benefit from Weight Loss

- Pulmonary disease
- Asthma
- Obstructive sleep apnea
- Hypoventilation syndrome
- Nonalcoholic fatty liver disease
- Steatosis
- Steatohepatitis
- Cirrhosis
- Gall bladder disease
- Reproductive abnormalities
  - Abnormal menses
  - Infertility
- Polycystic ovarian syndrome
- Osteoarthritis
- Skin
- Gout
- Idiopathic intracranial hypertension
- Stroke
- Cataracts
- Coronary heart disease
- Diabetes
- Dyslipidemia
- Hypertension
- Severe pancreatitis
- Cancer
  - Breast, uterus, cervix
  - Colon, esophagus, pancreas
  - Kidney, prostate
- Phlebitis
- Venous stasis
Bariatric Surgery: Long-Term Weight Loss and Decreased Mortality

- Swedish Obese Subjects (SOS) Study
- Up to 16 years follow-up
- Hazard ratio* = 0.76 (95% CI: 0.59–0.99), $P=0.04$

*Surgical group vs control group at 16 years
# Bariatric Surgery Reduces Diabetes, Cancer, and CV Mortality

<table>
<thead>
<tr>
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<th>Matched Subjects</th>
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<tbody>
<tr>
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<td>Surgery Group (n=7925)</td>
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<tr>
<td></td>
<td>No</td>
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<tr>
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</tr>
<tr>
<td>All deaths caused by disease</td>
<td>150</td>
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<tr>
<td>Cardiovascular diseases</td>
<td>55</td>
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<tr>
<td>Diabetes</td>
<td>2</td>
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<tr>
<td>Cancer</td>
<td>31</td>
</tr>
<tr>
<td>Other diseases</td>
<td>62</td>
</tr>
<tr>
<td>All non-disease causes</td>
<td>63</td>
</tr>
<tr>
<td>Accident unrelated to drugs</td>
<td>21</td>
</tr>
<tr>
<td>Poisoning of undetermined intent</td>
<td>9</td>
</tr>
<tr>
<td>Suicide</td>
<td>15</td>
</tr>
<tr>
<td>Other non-disease causes</td>
<td>18</td>
</tr>
</tbody>
</table>

Look AHEAD Trial – Diet and Lifestyle Did Not Reduce CV Endpoints but Did Improve Other Comorbidities

Main effect, -4 (95% CI, -5 to -3)

P<0.001

Look AHEAD — Was it Enough Weight Loss?
Improved Efficacy of Combined Lifestyle Intervention and Pharmacotherapy

In this trial the Lifestyle Modification was delivered by the MD
*Study was with Sibutramine, which is no longer available in the U.S

Adapted from Wadden TA, et al. NEJM. 2005;353:2111-2120.
# Recent Additions to Obesity Pharmacotherapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval</th>
</tr>
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<tbody>
<tr>
<td>Lorcaserin</td>
<td>• 5-HT\textsubscript{2C} serotonin agonist</td>
<td>• Approved, Summer 2012</td>
</tr>
<tr>
<td></td>
<td>• Little affinity for other serotonergic receptors</td>
<td></td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>• Sympathomimetic</td>
<td>• Approved, Summer 2012</td>
</tr>
<tr>
<td></td>
<td>• Anticonvulsant (GABA receptor modulation, carbonic anhydrase inhibition, glutamate antagonism)</td>
<td></td>
</tr>
</tbody>
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Lorcaserin: Those Who Lost ≥ 4.5% Total Body Weight by Week 12 Went on to Lose 10%
# Lorcaserin: Key Secondary Endpoints

## BLOOM Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lorcaserin</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Waist circumference (cm)</td>
<td>↓ -6.8</td>
<td>-3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP/DBP (mm Hg)</td>
<td>↓ -1.4 / -1.1</td>
<td>-0.8 / -0.6</td>
<td>0.04/0.01</td>
</tr>
<tr>
<td>Triglycerides (%)</td>
<td>↓ -6.15</td>
<td>-0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>↓ -2.0</td>
<td>-1.6</td>
<td>0.049</td>
</tr>
<tr>
<td>Beck depression II</td>
<td>-1.1</td>
<td>-0.9</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Intention-to-Treat Analysis with LOCF Imputation

## BLOOM-DM Study

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lorcaserin</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in HbA1C (%)</td>
<td>↓ -0.9</td>
<td>-0.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BLOOM-DM, Behavioral Modification and Lorcanserin for Obesity and Overweight Management in Diabetes Mellitus.
Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years: SEQUEL Study (completers)*

*Data from patients who completed 56 weeks on treatment (observed data, no imputation); P<.0001 vs placebo

Phentermine/Topiramate ER: Reductions in Rates of T2DM

Reductions of 70.5% and 78.7% in the annualized incidence rate of type 2 diabetes for those receiving 7.5/46 and 15/92, respectively – like DPP and getting closer to surgery.

Reprinted with permission from Garvey WT, et al. Diabetes Care. Published online before print, October 8, 2013.

Subanalysis of a Phase 3, randomized, placebo-controlled, double-blind study of overweight/obese subjects (BMI ≥27 to ≤45 kg/m²) with ≥2 comorbidities.
# Emerging Pharmacotherapies

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval/Phase</th>
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</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>• GLP-1 receptor agonist</td>
<td>• Phase 3 (3mg for obesity)</td>
</tr>
<tr>
<td>Naltrexone/Bupropion SR</td>
<td>• Dopamine/noradrenaline reuptake inhibitor</td>
<td>• NDA submitted, FDA requested CV outcomes study</td>
</tr>
<tr>
<td></td>
<td>• Opioid receptor antagonist</td>
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</tbody>
</table>
Liraglutide

- Glucagon-Like Peptide 1 (GLP-1) receptor agonist approved in 2010 for treatment of type 2 diabetes (1.8 mg/day)
- Phase III trials assessing effects of high dose (3.0 mg/day) to promote weight loss (SCALE trials)

Effect of Liraglutide on Body Weight in Overweight or Obese Subjects With Type 2 Diabetes: SCALE - Diabetes. 2011.
GLP-1 Modulates Numerous Functions in Humans

GLP-1: Secreted upon the ingestion of food

Promotes satiety and reduces appetite

Alpha cells: ↓ Postprandial glucagon secretion

Liver: ↓ Glucagon reduces hepatic glucose output

Stomach: Helps regulate gastric emptying

Beta cells: Enhances glucose-dependent insulin secretion

Liraglutide: Weight Loss Over 2 Years

All on liraglutide/placebo switched to liraglutide 2.4 mg at week 52, then between 70–96 weeks (shaded) to 3.0 mg

Liraglutide: Prevalence of Prediabetes at 1 and 2 years

**Prediabetes**

- *P≤0.0001 vs. placebo
- **P=0.005
- †P≤0.0002 vs. orlistat
- #P=0.01

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Orlistat</th>
<th>Liraglutide 1.2 mg</th>
<th>Liraglutide 1.8 mg</th>
<th>Liraglutide 2.4 mg</th>
<th>Liraglutide 3.0 mg</th>
<th>Liraglutide 2.4/3.0 mg pooled group</th>
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</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>36</td>
<td>29</td>
<td>33</td>
<td>36</td>
<td>36</td>
<td>31</td>
<td>37</td>
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<tr>
<td>Year 1</td>
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<td>Year 2</td>
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<td></td>
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<td></td>
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<td>16</td>
</tr>
</tbody>
</table>

Liraglutide 3 mg – Induced Weight Loss Following Hypocaloric Diet Run-In

Phase III: SCALE Maintenance Randomization Study

<table>
<thead>
<tr>
<th></th>
<th>Run-In</th>
<th>Treatment Period</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S</td>
<td>Liraglutide: n=207</td>
<td>Liraglutide: n=181</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo: n=206</td>
<td>Placebo: n=168</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>Liraglutide: n=156</td>
<td>Placebo: n=153</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo: n=144</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Liraglutide 3.0 mg: n=141</td>
</tr>
</tbody>
</table>

Mean ± SD weight at run-in (week – 12): 105.9 ± 22.1 kg

Mean percentage change in body weight and mean changes in vital signs from week −14 (screening) to week 68 (follow-up).

Summary

- Weight loss is now first line therapy for management of pre-diabetes and diabetes
- Weight loss improves multiple comorbid conditions
- Treatment selection depends upon BMI and is modified by patient’s risk profile
- New antiobesity medications have been approved and others are in-development
The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and "Well", Obese with Risk Factors, and Obese and "Sick"

Thursday, November 14, 2013

Course Chair
Ken Fujioka, MD
The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and “Well”, Obese with Risk Factors, and Obese and “Sick”

Case Presentations
Case 1

Case Description:

- Susan is a 52-year-old, newly single woman who comes in for weight management counseling. She gained her weight during a bad divorce several years ago. She is recently postmenopausal.

- She has two motivations: the first is to improve her tennis game (despite her size she plays doubles twice a week); the second is that she desires a better picture for her online dating profile. She tells you that she has always been a “big gal” with large hips and is a veteran of dieting.

- She takes no medications. Her mood is normal.
Case 1

Lab Data:
- BMI: 39 kg/m²
- A1C: 5.4%
- BP: 132/84 mm Hg
- HR: 80 bpm
- LDL-C: 105 mg/dL
- HDL-C: 62 mg/dL
- Triglycerides: 147 mg/dL
- Total Cholesterol: 196 mg/dL
Case Description:

- A 34-year-old, single woman with a history of major depression has noted rather significant weight gain since she was placed on antipsychotics along with her usual antidepressants.

- She is concerned about developing diabetes since her mother was just diagnosed with type 2 diabetes. She is not sexually active at this time.

- Her psychiatrist has just taken her off olanzapine (due to your advice), but the patient is still on a relatively high dose of an SSRI, which she needs to function.
Case 2

Lab Data:

- BMI: 33 kg/m²
- Waist circumference: 39 inches (slightly flat)
- A1C: 6.2%
- FBS: 125 mg/dL
- BP: 136/82 mm Hg
- HR: 92 bpm
- LDL-C: 94 mg/dL
- Total cholesterol: 174 mg/dL
- HDL-C: 50 mg/dL
- Triglycerides: 151 mg/dL
Case Description:

- A 55-year-old woman status post myocardial infarction 4 years ago comes in specifically asking if she can do anything about her weight.
- She is frustrated as she has tried multiple diets but struggles to stay on track. She gained most of her weight, which puts her in the obese category, after stopping cigarettes after her heart attack.
- She has had one episode of CHF 2 years ago and is starting to find mobility difficult with the increase in weight.
- She takes atorvastatin 20 mg daily, metoprolol 100 mg ER daily, lisinopril 20 mg daily, aspirin 81 mg daily.
Case 3

Lab Data:
- BMI: 36 kg/m²
- BP: 130/77 mm Hg
- Total cholesterol: 186 mg/dL
- LDL-C: 102 mg/dL
- HDL-C: 47 mg/dL
- Triglycerides: 187 mg/dL
- A1C: 6.5%
- FBS: 126 mg/dL
The Obesity Conundrum

Practical Approaches for Patients Who Are Obese and "Well", Obese with Risk Factors, and Obese and "Sick"

Question & Answer