AACE/ACE Consensus Conference on Obesity: Building an Evidence Base for Comprehensive Action

March 23–24, 2014

JW Marriott | Washington, DC
Purpose of the Conference

- Are we doing our best to reduce the suffering and social costs due to obesity?
- Do we have sufficient data to develop a concerted and comprehensive action plan – Can we do better?

Building an Evidence Base

Translation of the Evidence – Develop the Action Plan

Implementation
Pillars

Pillars Needed to Support a Concerted and Comprehensive Action Plan for the Prevention and Treatment of Obesity

1. Biomedical
2. Government & Regulatory
3. Health Industry & Economics
4. Organizations, Education & Research
Biomedical Pillar

W. Timothy Garvey, MD
Janet B. McGill, MD, FACE

Harold Bays, MD
Lynn Bufka, PhD
Alice Fuisz, MD, FACP
Angela Golden, DNP, FNP-c, FAANP
Lawrence Herman
John Jakicic, PhD
Suzanne Bennett Johnson, PhD
Sheela Magge, MD, MSCE, FAAP
David Marrero, PhD
Kenneth Miller, PhD, RN, CFNP, FAAN
John Morton, MD, MPH, FACS, FASMB
Hollie Raynor, PhD, RD, LDN
Adelaide Robb, MD, FAPA
Francesco Rubino, MD
Jennifer Seger, MD

Pillar Co-Moderator
Pillar Co-Moderator

National Lipid Association
American Psychological Association
American College of Physicians
American Association of Nurse Practitioners
American Academy of Physician Assistants
American College of Sports Medicine
American Psychological Association
American Academy of Pediatrics
Diabetes Center, Indiana University
American Association of Nurse Practitioners
American Society for Metabolic & Bariatric Surgery
Academy of Nutrition and Dietetics
American Psychiatric Association
American Society of Bariatric Physicians
Government & Regulatory

Jeffrey I. Mechanick, MD, FACN, FACP, FACE  Pillar Co-Moderator
Jonathan D. Leffert, MD, FACP, FACE  Pillar Co-Moderator

Ann Albright, PhD, RD  Centers for Disease Control and Prevention
Patricia Beaston, MD, PhD  US Food and Drug Administration, Office of Device Evaluation
Helene D. Clayton-Jeter, OD  US Food and Drug Administration, Office of Constituent Affairs
Jackie Haven, MS, RD  US Department of Agriculture, Center for Nutrition Policy and Promotion
Joseph Hutter, MD, MA  Centers for Medicaid & Medicare Services
Susan Kansagra, MD, MBA  Health Promotion & Disease Prevention, NYC Department of Health and Mental Hygiene
Elizabeth Koller, MD, FACE  Centers for Medicaid & Medicare Services
Gregory Peterson, DO, FACP  American Assoc of Clinical Endocrinologists
Health Industry & Economics

Alan J. Garber, MD, PhD, FACE
Daniel Einhorn, MD, FACP, FACE
Pillar Co-Moderator
Pillar Co-Moderator

Paulos Berhanu, MD, FACE
Jason Brett, MD
Elaine Chiquette, BPharm, PharmD
Brian Eckley
Eric Andrew Finkelstein, PhD
Todd Hobbs, MD

Takeda Pharmaceuticals U.S.A., Inc.
Novo Nordisk Inc.
GI Dynamics, Inc.
Eisai Inc.
Duke - NUS Graduate Medical School
Novo Nordisk Inc.

Bank of America
IMS Health
Takeda Pharmaceuticals U.S.A., Inc.
Weight Watchers International
Humana
Southwest Airlines Co.
Cigna
Aetna
GI Dynamics, Inc.

Kenneth Snow, MD
Kembre Roberts
Robert Silverman, MD, FACE
Karen Miller-Kovach, MBA, MS, RD
Andrew Renda, MD, MPH

Humana
Southwest Airlines Co.
Cigna
Aetna
GI Dynamics, Inc.

Barbara Troupin, MD, MBA
Mansi Mehta, RD, LDN
Jim Huffman
Matthew Maryniak, MBA
Mansi Mehta, RD, LDN

VIVUS, Inc.
<table>
<thead>
<tr>
<th>Organization/Role</th>
<th>Name/Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>George Grunberger, MD, FACE, FACE</td>
<td>Pillar Co-Moderator</td>
</tr>
<tr>
<td>Yehuda Handelsman, MD, FACP, FACE</td>
<td>Pillar Co-Moderator</td>
</tr>
<tr>
<td>Solveig Cunningham, PhD</td>
<td>Rollins School of Public Health, Emory University</td>
</tr>
<tr>
<td>Ann Danoff, MD</td>
<td>Association of Program Directors in Endocrinology, Diabetes &amp; Metabolism</td>
</tr>
<tr>
<td>Scott Kahan MD, MH</td>
<td>STOP Obesity Alliance</td>
</tr>
<tr>
<td>Mary Lieh-Lai MD, FAAP, FCCP</td>
<td>Accreditation Council for Graduate Medical Education</td>
</tr>
<tr>
<td>Lillian Lien MD</td>
<td>Duke Inpatient Diabetes Management</td>
</tr>
<tr>
<td>Joe Nadglowski</td>
<td>Obesity Action Coalition</td>
</tr>
<tr>
<td>Chiadi Nduemele, MD, MHS</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>Robert Ratner, MD, FACE</td>
<td>American Diabetes Association</td>
</tr>
<tr>
<td>Laura Ritzenthaler</td>
<td>American College of Cardiology</td>
</tr>
</tbody>
</table>
Five Questions

1. What is obesity?
2. What options are available for obesity management?
3. What is the optimal use of therapeutic modalities?
4. Can the optimal framework be cost-effective?
5. What are the knowledge gaps and how can they be filled?
AACE Perspective: Obesity as a Disease
1. “It is the strong contention of AACE that the view of obesity as a behavioral decision is debunked by biomedical evidence.”

2. “…obesity is a primary disease, and the full force of our medical knowledge should be brought to bear on the prevention and treatment of obesity as a primary disease entity.”

3. “…obesity is an altered physiological and metabolic state, with genetic, environmental, and behavioral determinants, which results in increased morbidity and mortality.”

Is Obesity a Disease?

Concordance of Body Type between Dizygotic or Fraternal Twins

Concordance of Body Type between Monozygotic or Identical Twins
Polygenetic Basis of Obesity

1. Nearly 100 genes have been identified that place people at increased risk of obesity (i.e., ‘polygenic’)

Examples of Obesity Susceptibility Genes
- MAP2K3, NEGR1, TMEM18, GNPDA2, MTCH2, SH2B1, FTO, MC4R, KCTD15, TNNI3K, PTBP2, SEC16B, FANCL, LRP1B, RBJ, CADM2, ETV5/DGKG, SLC39A8, POC5, ZNF608, TFAP2B, LINGO2, LMX1B, RPL27A, BDNF, MTCH2, BDCDIN3D, MTIF3, PRKD1, NRXN3, MAP2K5, GPR5B, ATXNL2, KCTD15, QCPTL, ZC3H4

2. Each of these genes convey only a very small relative risk for the disease

3. People who inherit greater numbers of these susceptibility genes are the ones that will be relatively obese in any given environment.

BMI Increases in Individuals with Greater Numbers of Susceptibility Genes

Energy intake
Ingestion of:
Proteins
Fats
Carbohydrates

Human being: biological and behavioral interface

Energy expenditure
Basal metabolic rate
Physical activity
Energy to metabolized food

Cause of Obesity: Abnormal Energy Balance

Body Weight

Increase
Decrease
OVERFEEDING – Weight Gain

UNDER FEEDING – Weight Loss

100-day overfeeding protocol in 12 pairs of male identical twins

28-day very low calorie diet in 14 pairs of identical female twins
Polygenic Diseases: Susceptibility Genes Interact with Each Other and the Environment.
AACE Position on Obesity: gene : environment : behavior interactions

<table>
<thead>
<tr>
<th>Genetic</th>
<th>Environmental</th>
<th>Behavioral</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Large subsets of at-risk genes, which</td>
<td>- Built environment</td>
<td>- Poor health literacy or decision-making</td>
</tr>
<tr>
<td>together enhance overall obesity risk</td>
<td>- Sociocultural attitudes and customs</td>
<td>- Diet preferences</td>
</tr>
<tr>
<td>- These and other subsets of genes influence</td>
<td>- Limited availability of fresh food</td>
<td>- Sedentary lifestyle</td>
</tr>
<tr>
<td>effects of obesity on metabolism,</td>
<td>- Environmental endocrine disruptors</td>
<td>- Food-seeking behavior related to</td>
</tr>
<tr>
<td>insulin resistance, and glucose</td>
<td></td>
<td>psychological conditions</td>
</tr>
<tr>
<td>tolerance</td>
<td></td>
<td>(depression, anxiety, etc.)</td>
</tr>
</tbody>
</table>

Rising Rates of Obesity but Not Overweight in US Adults

Note: Age-adjusted by the direct method to the year 2000 US Bureau of the Census using age groups 20–39, 40–59, and 60–74 years. Pregnant females excluded. Overweight defined as 25 ≤ BMI < 30; obesity defines BMI ≥30; extreme obesity defines as BMI ≥40.

Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey (NHANES) data.
Number (in Millions) With Diagnosed Diabetes, United States, 1980–2009

Civilian, Non-Institutionalized Persons
Centers for Disease Control and Prevention. NHANES Data. Updated April, 2011.
AMA: Essential Criteria of a Disease

1. Characteristic signs or symptoms
2. Impairment in the normal functioning of some aspect of the body
3. Results in harm or morbidity

Available at: http://www.ama-assn.org/resources/doc/csaph/a05csa4-fulltext.pdf
Characteristic signs or symptoms

- Body Mass Index (kg body weight / meters in height squared)
- Waist Circumference
- Obesity-Related Complications
## WHO Classification of Obesity by BMI, Waist Circumference, and Disease Risk

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI (kg/m²)</th>
<th>Co-morbidity Risk</th>
<th>Waist Circumference &amp; Co-morbidity Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Low but other problems</td>
<td></td>
</tr>
<tr>
<td>Normal Weight</td>
<td>18.5 – 24.9</td>
<td>Average</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25 – 29.9</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30 – 34.9</td>
<td>Moderate</td>
<td>High</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35 – 39.9</td>
<td>Severe</td>
<td>Very High</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥40</td>
<td>Very severe</td>
<td>Extremely High</td>
</tr>
</tbody>
</table>

Men ≤40 in
Women ≤35 in

Men >40 in
Women >35 in


Impairment in the normal functioning of some aspect of the body

✓ Brain
✓ Fat
Control of Appetite

Factors from tissues that reflect fuel availability

Brain (hypothalamus)

Brain (higher centers)

Orexigenic (eat more)

Stomach

Fat

Intestines

Pancreas

Stimulate Appetite

Anorexigenic (eat less)

NPY

LEPTIN

GHRELIN

CCK

GLP-1

PYY

AMYLIN

INSULIN

Reduce Appetite

Stimulate Appetite
In Obesity, biology protects against weight loss and maintains a high body weight.

- ↑ Ghrelin
- ↓ Leptin, PYY, CCK, Amylin
- ↓ Resting energy expenditure
- ↑ Hunger
- ↑ Calorie-dense food preferences

Baseline weight: 250 lbs

Weight Loss

Weight Gain
In Obesity, fat tissue can be inflamed (i.e., “sick fat”) and function abnormally.

Fat Tissue Inflammation

Ventral Adiposity

ABNORMAL SECRETION OF ADIPOCYTE FACTORS

LIPIDS in BLOOD
Dyslipidemia

BLOOD VESSEL
Hypertension
Atherosclerosis

MUSCLE
Insulin resistance
Glucose intolerance

LDL=low-density lipoprotein; VLDL=very-low-density lipoprotein.
The Spectrum of Cardiometabolic Disease

Prediabetic States

1. Prediabetes
   i. IFG
   ii. IGT

2. Metabolic Syndrome
   - waist
   - blood pressure
   - fasting glucose
   - triglycerides
   - HDL-cholesterol

Type 2 Diabetes

Cardiovascular Disease
Results in harm or morbidity

- Cardiometabolic Disease Complications
  (diabetes, cardiovascular)
- Biomechanical Complications
- Mortality
Medical Complications of Obesity

Obesity

- Depression
- Cancer
- Gallbladder Disease

Prediabetic States

- Dyslipidemia
- Hypertension

Diabetes

- CVD

Cardiometabolic Disease

Other Complications

- Sleep Apnea
- Osteoarthritis
- Stress Incontinence
- GERD
- Dismobility/Disability

BioMechanical Complications

Other Complications

Prediabetic States

- Dyslipidemia
- Hypertension

Diabetes

- CVD

Cardiometabolic Disease

Chronic Disease Model

(ie, obesity, diabetes, asthma, hypertension, lupus, etc.)
Domenica M. Rubino, MD.
AMA: Essential Criteria of a Disease

1. Characteristic signs or symptoms
2. Impairment in the normal functioning of some aspect of the body
3. Results in harm or morbidity


Available at: http://www.ama-assn.org/resources/doc/csaph/a05csa4-fulltext.pdf
## Weight Loss Improves Obesity Complications

<table>
<thead>
<tr>
<th>OBESITY COMPLICATION</th>
<th>% weight loss required to benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes (HbA1c)</td>
<td>3% to &gt;15%</td>
</tr>
<tr>
<td>Diabetes Prevention</td>
<td>3% to 10%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5% to &gt;15%</td>
</tr>
<tr>
<td>Dyslipidemia, (↑TG / ↓HDL-c)</td>
<td>3% to &gt;15%</td>
</tr>
<tr>
<td>Sleep Apnea</td>
<td>≥10%</td>
</tr>
<tr>
<td>Fatty Liver Disease</td>
<td>10%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>5-10%</td>
</tr>
<tr>
<td>Stress Incontinence</td>
<td>5-10%</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>5-10% women, 10% men</td>
</tr>
<tr>
<td>Polycystic Ovary Syndrome</td>
<td>5-15% (&gt;10% optimal)</td>
</tr>
</tbody>
</table>

How Do We Use Available Treatment Modalities for Overweight and Obese Patients?

- Balance efficacy, safety, and cost
- Optimize benefit: risk ratio
- Achieve best outcomes
- Cost-effectiveness of care
Intensification of Lifestyle Therapies to Achieve Weight Loss Goals

**Lifestyle Therapy**

- Simple advice to lose weight in doctor’s office
- Internet programs or self-help books
- Advice from dietitian
- Structured programs (Weight Watchers, YMCA, telecommunication)
- Multidisciplinary structured programs
- Physician-driven individualized structured programs

**Impart skills and behavior change to induce and maintain weight loss**
12-month net weight change (kg):

- Gardner, JAMA, 2007
  297:969-77
Adherence Is More Important Than Diet Type for Weight Loss Success

Weight Change by Diet Type

Weight Change by Dietary Adherence

Remember the Pathophysiology of Obesity: mechanisms protecting against weight loss

It is difficult for patients to maintain their weight loss over time.

Sacks FS. et al. *NEJM* 2009;360(9) 859-873.
## Obesity Pharmacotherapy

<table>
<thead>
<tr>
<th>Agents</th>
<th>Action</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previously available</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine</td>
<td>• Decreases appetite</td>
<td>• 1959</td>
</tr>
<tr>
<td>Orlistat</td>
<td>• Decrease fat absorption in gut</td>
<td>• 1997</td>
</tr>
<tr>
<td><strong>Recently Approved</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentermine/Topiramate ER</td>
<td>• Decreases appetite</td>
<td>• Summer 2012</td>
</tr>
<tr>
<td>Lorcaserin</td>
<td>• Decreases appetite</td>
<td>• Summer 2012</td>
</tr>
<tr>
<td><strong>Available in Future? (2014)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion/Naltrexone</td>
<td>• Decrease appetite</td>
<td>• FDA requested CV outcomes study</td>
</tr>
<tr>
<td>Liraglutide high dose (3 mg/d)</td>
<td>• Decreases appetite</td>
<td>• Phase 3 finished • FDA pending</td>
</tr>
</tbody>
</table>
Combined Lifestyle Intervention and Pharmacotherapy

Bariatric Surgery & Devices

**Devices**
- Stomach implants
- Gastric stimulation
- Duodenal barrier

**Laparoscopic Sleeve Gastrectomy (LSG)**

**Laparoscopic Adjustable Gastric Band (LABG)**

**Roux-en-Y Gastric Bypass (RYGB)**
## NHLBI Obesity Treatment Guidelines

### A Guide to Selecting Treatment

<table>
<thead>
<tr>
<th>BMI Category</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>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet, physical activity, and behavior</td>
<td>Appropriate NHLBI Guidelines +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Pharmacotherapy</td>
<td>No</td>
<td>With comorbidities +</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Surgery*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No LAGB only</td>
<td>With comorbidities</td>
</tr>
</tbody>
</table>

* *Bariatric surgeries require lifestyle medical follow-up.*

†FDA approved gastric band surgery for patients with BMI ≥30 and one weight related medical condition (February 2011).

Complications-centric Model for Obesity Care

**STEP 1** EVALUATION FOR COMPLICATIONS AND STAGING

- **CARDIOMETABOLIC DISEASE**
  - NO COMPLICATIONS
    - BMI 25–26.9, or BMI ≥ 27
  - BIOMECHANICAL COMPLICATIONS
    - BMI ≥ 27 WITH COMPLICATIONS
      - Stage Severity of Complications
        - LOW
        - MEDIUM
        - HIGH

**STEP 2** SELECT:

- Lifestyle Modification: MD/RD counseling; web/remote program; structured multidisciplinary program
- Medical Therapy: phentermine; orlistat; lorcaserin; phentermine/topiramate ER
- Surgical Therapy (BMI ≥ 35): Lap band; gastric sleeve; gastric bypass

**STEP 3**

If therapeutic targets for improvements in complications not met, intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss

Cardiometabolic Disease Staging: Predicts who will get diabetes in CARDIA Study

No drugs are currently approved for the treatment of pre-diabetes.

Recommendation 5

• Advise your patients with BMI > 35 and a co-morbidity or > 40 that bariatric surgery may be an appropriate option to improve health and offer referral to an experienced bariatric surgeon for consultation and evaluation.


Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*

☑ Metformin
☑ GLP-1 RA
☑ DPP4-i
☑ AG-i
⚠️ SGLT-2
⚠️ TZD
⚠️ SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

GLP-1 RA
DPP4-i
TZD
** SGLT-2
Basal insulin
Colecobalamin
Bromocriptine QR
AG-i
SU/GLN

MET or other first-line agent
If not at goal in 3 months proceed to triple therapy

TRIPLE THERAPY*

If not at goal in 3 months proceed to or intensify insulin therapy

ENTRY A1c > 9.0%

NO SYMPTOMS
DUAL THERAPY
OR
TRIPLE THERAPY

SYMPTOMS
INSULIN ± OTHER AGENTS

ADD OR INTENSIFY INSULIN

PROGRESSION OF DISEASE

* Order of medications listed are a suggested hierarchy of usage
** Based upon phase 3 clinical trials data

LEGEND
☑ = Few adverse events or possible benefits
⚠️ = Use with caution

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Obese persons face discrimination in ...

- EMPLOYMENT
- COLLEGE ADMISSION
- ROMANCE
- MEDICAL CARE
- INCOME
- AIRLINE SEATING

>90% of obese persons have attempted to lose weight
>50% are currently trying to lose weight

"We are caught in an inescapable network of mutuality, tied in a single garment of destiny. Whatever affects one directly, affects all indirectly" (16 April 1963, Birmingham).
AACE/ACE Consensus Conference on Obesity: Building an Evidence Base for Comprehensive Action

March 23–24, 2014
JW Marriott | Washington, DC
Keynote Speaker

John Foreyt, PhD

Director, Behavioral Medicine Research Center at Baylor College of Medicine
Professor, Department of Medicine, Baylor College of Medicine
Keynote Speaker

Patrice A. Harris, MD
American Medical Association Board of Trustees
Director, Health Services for Fulton County, Georgia
Keynote Speaker

Lawrence A. Soler, Esq
President and CEO, Partnership for a Healthier America
Now we get to work:

AACE Position Statement

“…the full force of our medical knowledge should be brought to bear on the prevention and treatment of obesity…”

Building an evidence base for a comprehensive action plan for the prevention and treatment of obesity in America.
Sunday Afternoon

‘Within’ Pillar Break-Out Discussions

Constituencies within each Pillar examine data and discuss answers to the 5 questions.

• What is the evidence base?
• Where is there consensus?
• Where are there disagreements?
• What are the knowledge gaps?
Monday Morning

‘Among’ Pillar Discussions

Pillars examine data and discuss answers to 5 questions together

- What is the evidence base?
- Where is there consensus?
- Where are there disagreements?
- What are the knowledge gaps?
“We are caught in an inescapable network of mutuality, tied in a single garment of destiny. Whatever affects one directly, affects all indirectly" (16 April 1963, Birmingham).