Why Do We Treat Obesity?

Organ-Specific, Hormonal, and Biomechanical Complications

AACE OBESITY RESOURCE CENTER

AACE ONLINE ENDOCRINE ACADEMY

3. Treatment Based on Clinical Judgment

TREATMENT GOALS BASED ON DIAGNOSIS IN THE MEDICAL MANAGEMENT OF PATIENTS WITH OBESITY

	DIAGNOSIS		TREATMENT GOALS	
	Anthropometric Component	**Clinical Component**	**Intervention/ Weight-Loss Goal**	**Clinical Goals**
TERTIARY PREVENTION				
Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Polycystic ovary syndrome	5% to 15% or more	• Ovulation • Regularization of menses • Reduced hirsuitism • Enhanced insulin sensitivity • Reduced serum androgen levels
		Female infertility	10% or more	• Ovulation • Pregnancy and live birth
		Male hypogonadism	5% to 10% or more	Increase in serum testosterone
		Obstructive sleep apnea	7% to 11% or more	• Improved symptomatology • Decreased apnea-hypopnea index
		Asthma/reactive airway disease	7% to 8% or more	• Improvement in forced expiratory volume at 1 second • Improved symptomatology
		Osteoarthritis	• ≥10% • 5% to 10% or more when coupled with exercise	• Improvement in symptomatology • Increased function
		Urinary stress incontinence	5% to 10% or more	Reduced frequency of incontinence episodes
		Gastroesophageal reflux disease	10% or more	Reduced symptom frequency and severity
		Depression	Uncertain	• Reduction in depression symptomatology • Improvement in depression scores

Abbreviations: A1C = hemoglobin A1c; BMI = body mass index; BP = blood pressure; HDL-C = high-density lipoprotein cholesterol; T2DM = type 2 diabetes mellitus.

Organ-Specific, Hormonal, and Biomechanical Complications

Gallbladder Disease

The Paradox of Obesity and Gallbladder Disease

Effect of Obesity

- Increased risk of cholesterol gallstones, cholecystis, and gallbladder cancer, especially in women
  - Increased biliary fat may increase cholesterol in the gallbladder
- Risk increases with higher BMI

Effect of Weight Loss

- Increased risk of gallstones
  - 10% to 25% of patients on diet-exercise regimens and up to 30% undergoing bariatric surgery develop gallstones
  - Higher risk in patients with a high BMI prior to weight loss or those who lose weight rapidly
- Oral ursodeoxycholic acid during weight loss may prevent gallstone formation

BMI = body mass index.

Everhart JE. *Ann Intern Med*. 1993;119:1029-1035. Erlinger S. *Eur J Gastroenterol Hepatol*. 2000;12:1347-1352.
Pitt HA. *HPB (Oxford).* 2007;9:92-97.

Organan-Specific, Hormonal, and Biomechanical Complications

Sex Hormone Disorders

Polycystic Ovary Syndrome

Disease Features

- Characterized by anovulation or irregular menstrual cycles with hyperandrogenism
  - Not a consequence of obesity, but may worsen with weight gain
  - Pathophysiologically linked to insulin resistance
- Increased risk for T2D, dyslipidemia, hypertension, inflammation, and CVD

Treatment

- Increase insulin sensitivity
  - Aerobic exercise and weight loss
  - Metformin,* pioglitazone,*† or GLP-1 receptor agonist*†
- Spironolactone or other nonandronergic oral contraceptive for skin manifestations (hirsutism, acne)

*Not FDA-approved for PCOS.

†Recommended only for women with IGT or T2D. Pregnancy category C—use with contraception in women of childbearing age.

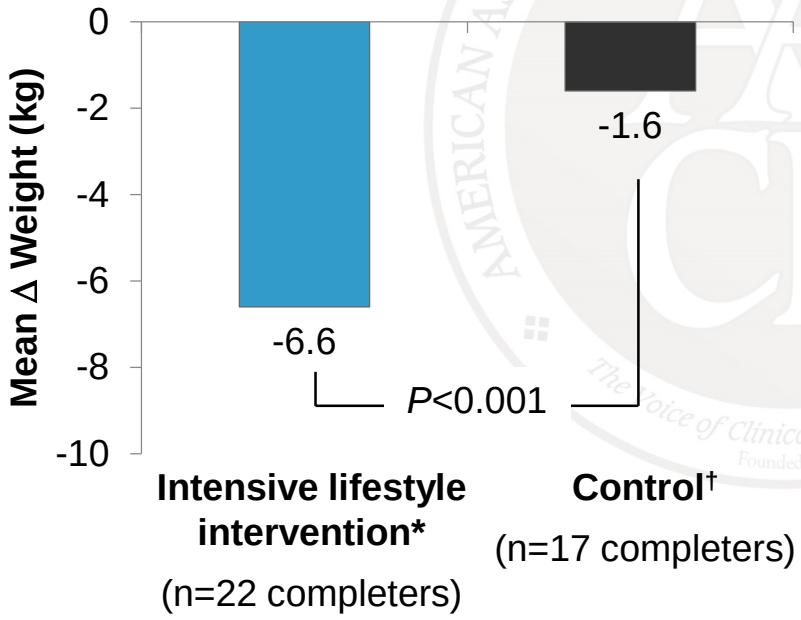
CVD = cardiovascular disease; PCOS = polycystic ovary syndrome; T2D = type 2 diabetes.

Cobin RH, et al. *Endocr Pract*. 2005;11:126-134..

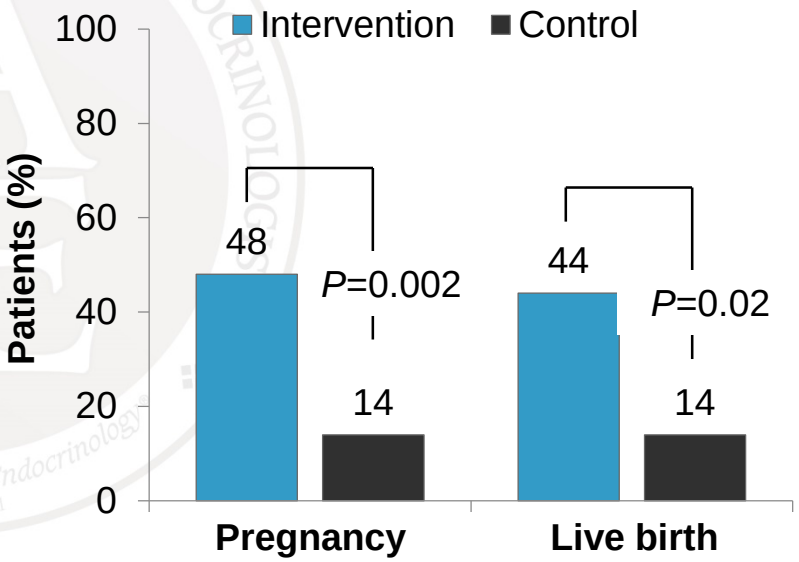
Effect of Weight Loss on Female Infertility

Women With Obesity Presenting for Fertility Treatment (N=49)

Weight Change After 12 Weeks



Pregnancy Outcomes



*Very-low-energy diet for first 6 weeks followed by a hypocaloric diet for next 6 weeks, with weekly multidisciplinary group meetings.

† Weight loss recommendations plus the same printed materials as intervention group.

Sim KA, et al. *Clin Obes*. 2014;4:61-68.

Obesity and Testosterone Deficiency

Disease Features

- Total testosterone <280-300 ng/dL and/or free testosterone <5-9 ng/dL*
- Signs and symptoms: fatigue, decreased libido, ED, altered mood/cognition, decreased muscle mass and BMD, increased fat mass
- Strongly associated with metabolic syndrome
- Increased risk for T2D, dyslipidemia, hypertension, and CVD

Treatment

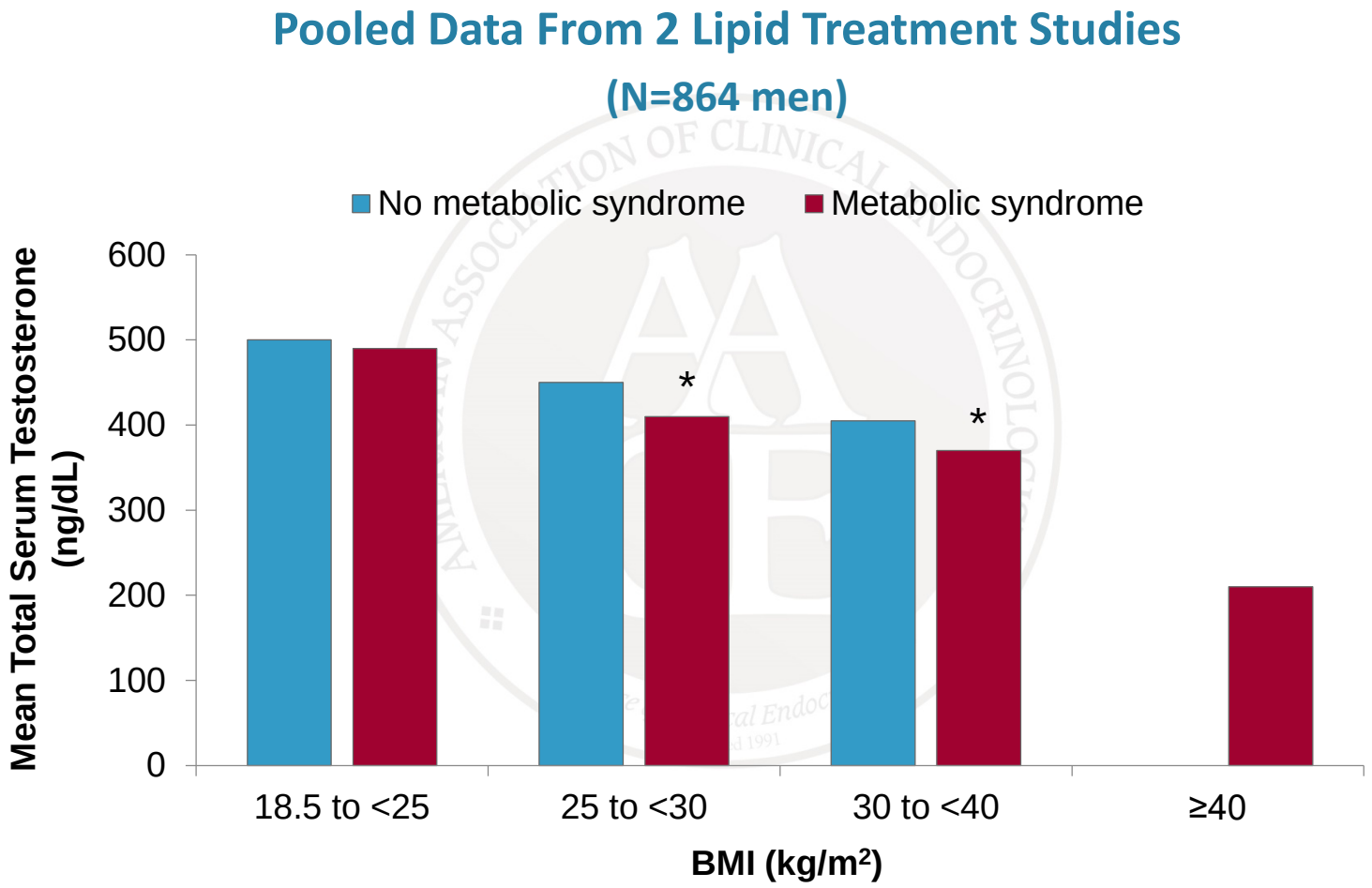
- Weight loss
- Testosterone replacement therapy

*Reference range varies with laboratory; use lower limit of normal.

BMD = bone mineral density; CVD = cardiovascular disease; ED = erectile dysfunction; T2D = type 2 diabetes.

Bhasin S, et al. *J Clin Endocrinol Metab*. 2010;95:2536-2559. Corona G, et al. *Eur J Endocrinol*. 2013;168:829-843.

Androgen Deficiency and BMI



*P<0.05 vs no metabolic syndrome.

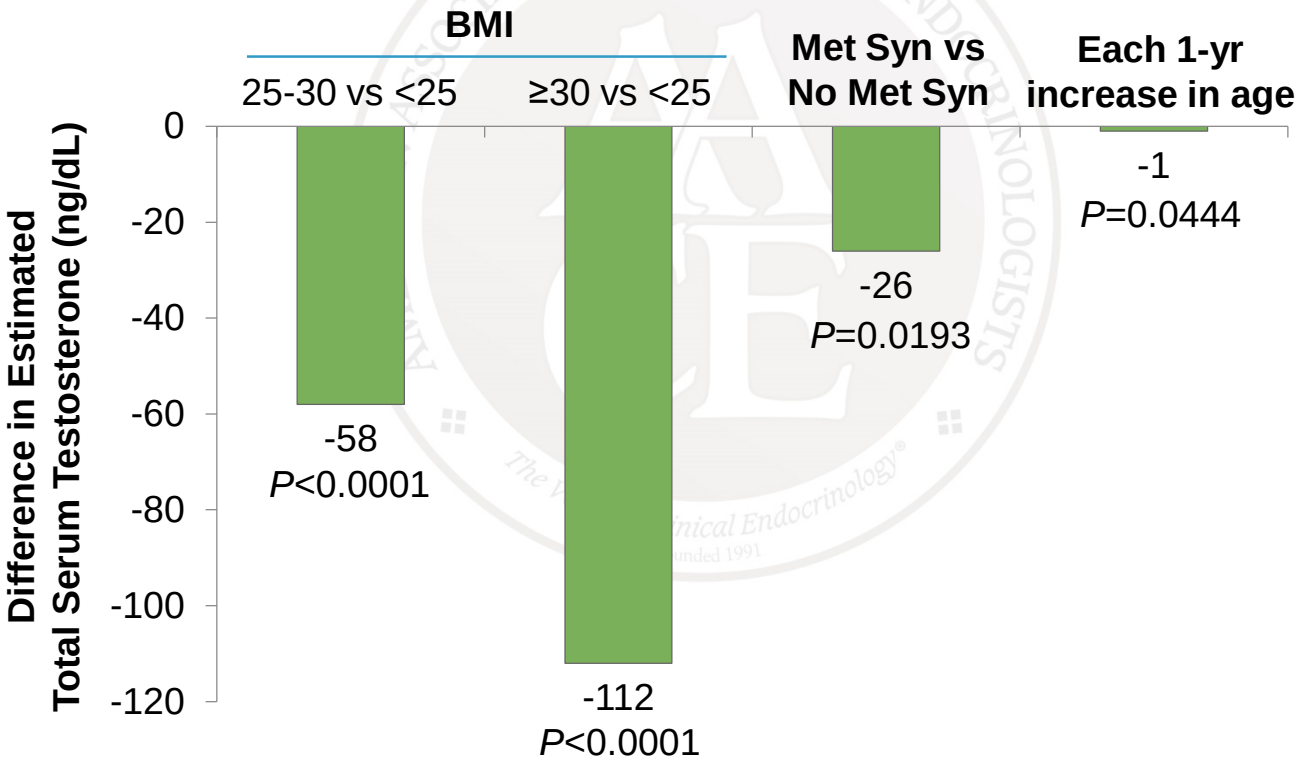
BMI = body mass index.

Kaplan SA, et al. *J Urol*. 2006;176:1524-1527.

Effects of Obesity, Metabolic Syndrome, and Age on Testosterone Levels

Multiple Linear Regression Analysis

(N=864 men participating in 2 lipid treatment studies)



BMI = body mass index, in kg/m^2; Met Syn = metabolic syndrome.

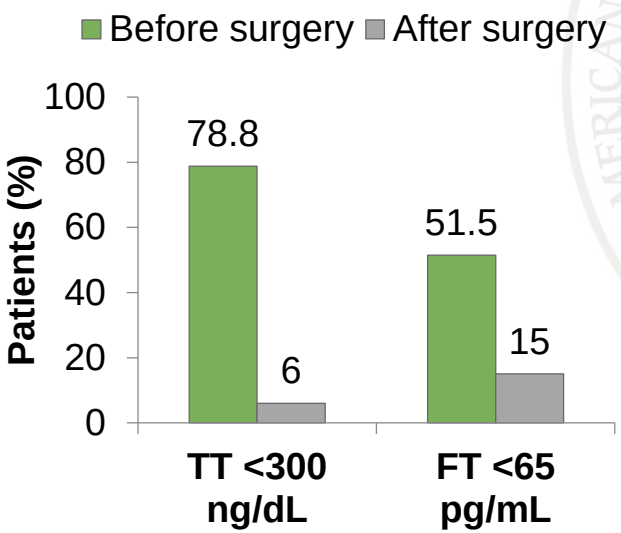
Kaplan SA, et al. *J Urol*. 2006;176:1524-1527.

Effect of Weight Loss on Male Hypogonadism

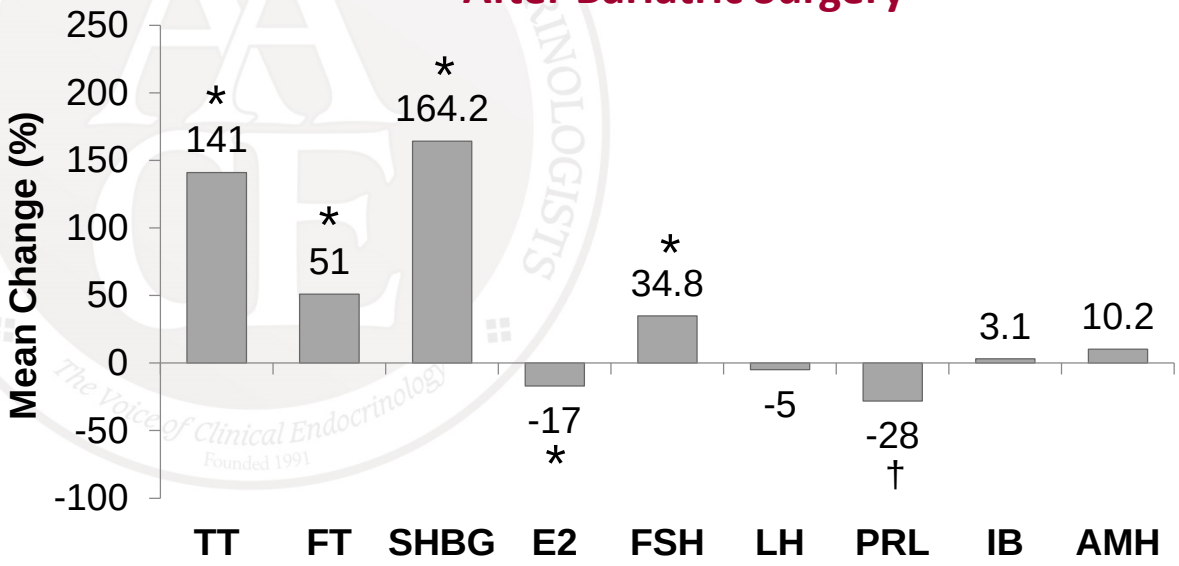
Observational Data

(N=33 men, mean WL = 18.8% [59.1 kg])

Hypogonadism Before and 12 Months After Bariatric Surgery



Change in Sex Hormones 12 Months After Bariatric Surgery



*P<0.001, † P=0.01 vs value before surgery.

AMH = anti-Müllerian hormone; E2 = estradiol; FSH = follicle-stimulating hormone; FT = free testosterone ; IB, inhibin B; LH = luteinizing hormone; PRL = prolactin; SHBG = sex hormone binding globulin; TT = total testosterone; WL = weight loss.

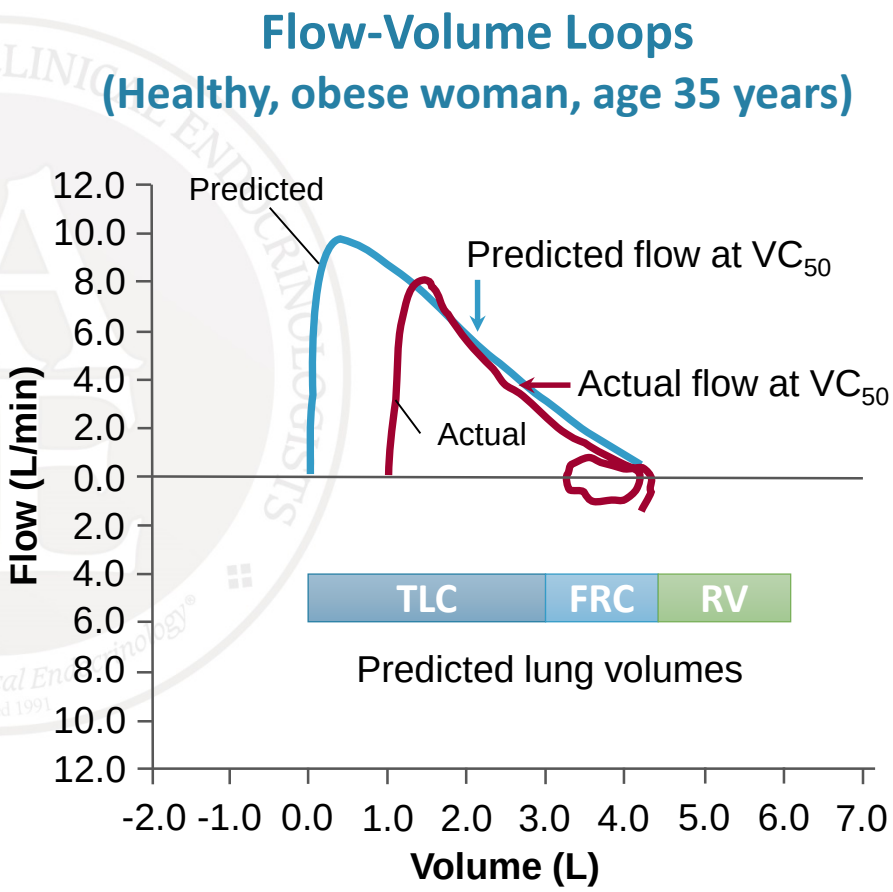
Pellitero S, et al. *Obes Surg*. 2012;22:1835-1842.

Organan-Specific, Hormonal, and Biomechanical Complications

Pulmonary Disorders

Obesity Adversely Affects Lung Function

- Stiffening of total respiratory system
  - Reduced lung and chest wall compliance
  - Reduced tidal volume and short, rapid breathing pattern
- Reduced lung volume and vital capacity
- Increased risk of airway closure and ventilation distribution abnormalities



FRC = functional residual capacity; RV = reserve volume; TLC = total lung capacity; VC = vital capacity.

Salome CM, et al. *J Appl Physiol.* 2010;108:206-211.

Obstructive Sleep Apnea

Mechanisms

- Feedback loop involving interplay between excess visceral adipose tissue, insulin resistance, and inflammatory cytokines
  - Excess fat reduces diaphragm mobility and promotes soft tissue edema, which in turn lead to depression of ventilation
- Ventilation depression causes sleep apnea and poor sleep, which contributes to daytime sleepiness and fatigue
- Poor sleep promotes stress hormone and interleukin 6 production, which exacerbates insulin resistance

Risk Factors

- Obesity
- Neck circumference >44 cm
- Narrowed airway
- Hypertension
- Smoking
- Male sex
- Age
- Family history
- Alcohol or sedatives

Treatment Options

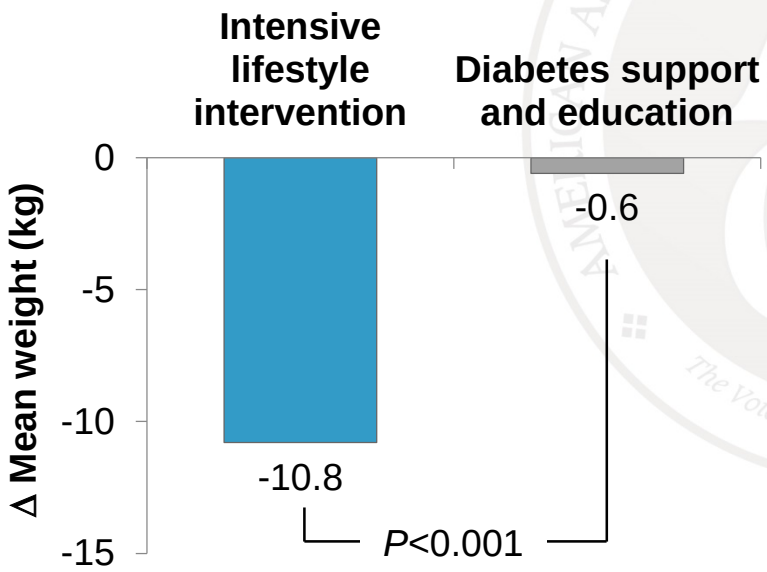
- Continuous positive airway pressure (CPAP)
- Adjustable airway pressure devices
- Oral appliances
- Surgery
  - Uvulopalatopharyngoplasty (UPPP)
  - Maxillomandibular advancement
  - Tracheostomy

Epstein LJ, et al. *J Clin Sleep Med*. 2009;5:263-276. NHLBI Working Group on Sleep Apnea. *Am Fam Physician*. 1996;53:247-253. Vgontzas AN, et al. *J Intern Med*. 2003;254:32-44 .

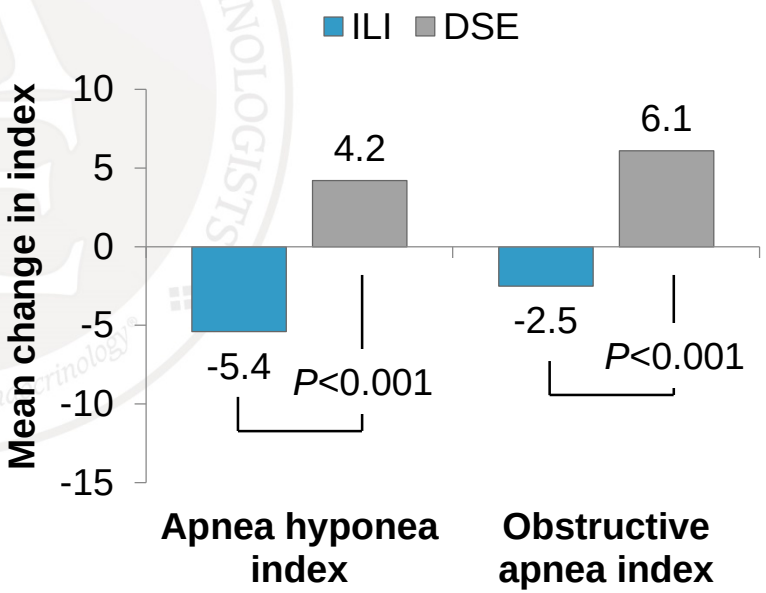
Effect of Weight Loss on OSA

Sleep AHEAD Study
(N=264 Patients With T2D)

Weight Change After 12 Months



Change in OSA After 12 Months



DSE = diabetes support and education; ILI = intensive lifestyle intervention.

Foster GD, et al. *Arch Intern Med*. 2009;169:1619-1626.

Effects of Weight Loss on Asthma and Reactive Airway Disease

- Calorie restriction with an average of 8% weight loss associated with improvements in asthma disease factors
  - Asthma symptoms
  - Quality of life
  - Peak expiratory flow
  - Markers of oxidative stress and inflammation
- After RYBG (WL ~23%), significant reductions in expression of:
  - Asthma-related genes
    - Interleukin-4
    - Disintegrin
    - Metalloproteinase 33
  - Rumor necrosis factor (ligand) superfamily member 14
  - Matrix metallopeptidase-9
  - C-C chemokine receptor type-2
  - Nitric acid metabolites

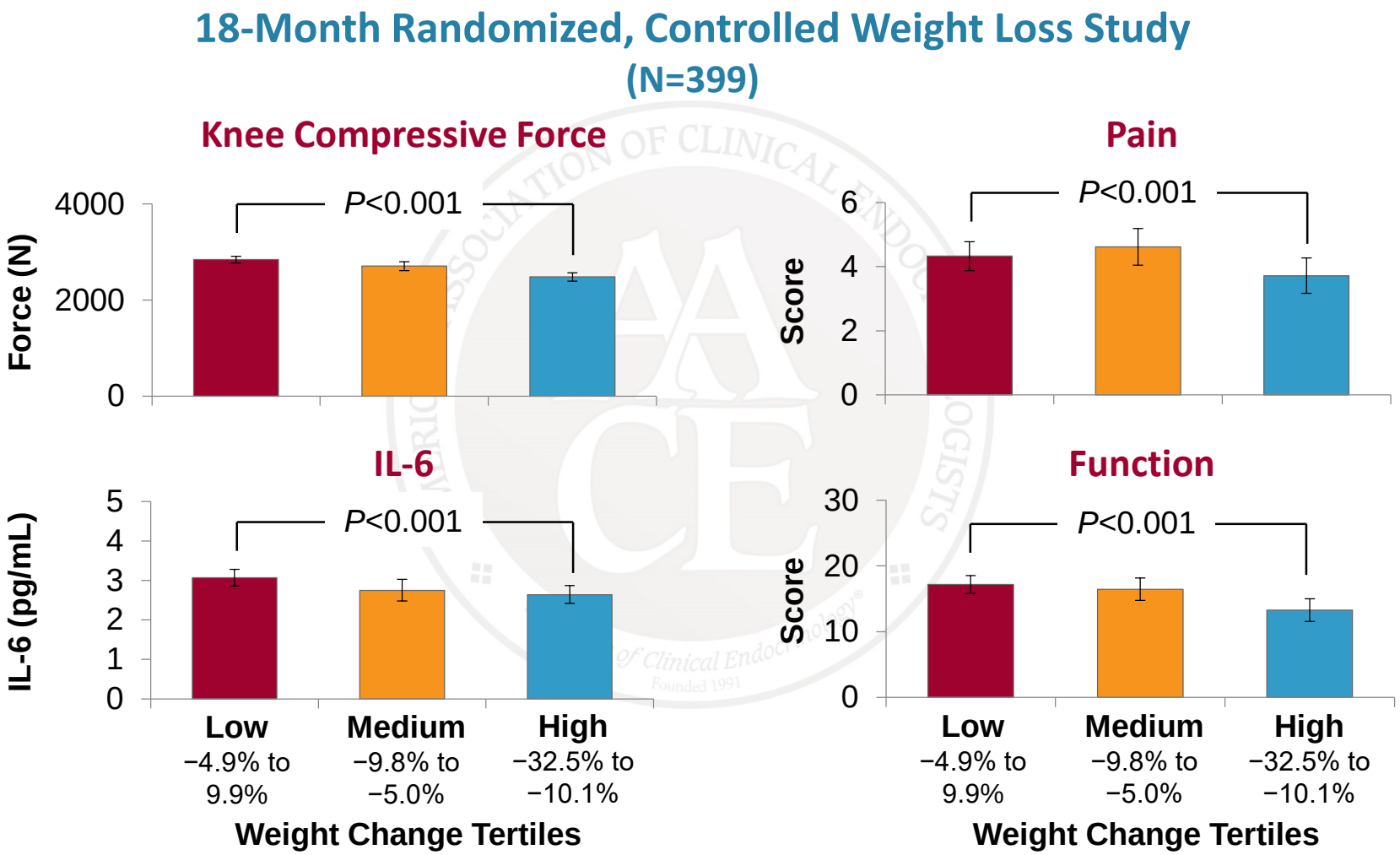
RYGB = Roux-en-Y gastric bypass; WL = weight loss.

Johnson JB, et al. *Free Radic Biol Med*. 2007;42(5):665-674. Dandona P, et al. *Obesity*. 2014;22(2):356-362.

Organan-Specific, Hormonal, and Biomechanical Complications

Biomechanical Disorders

Effect of Weight Loss on Osteoarthritis

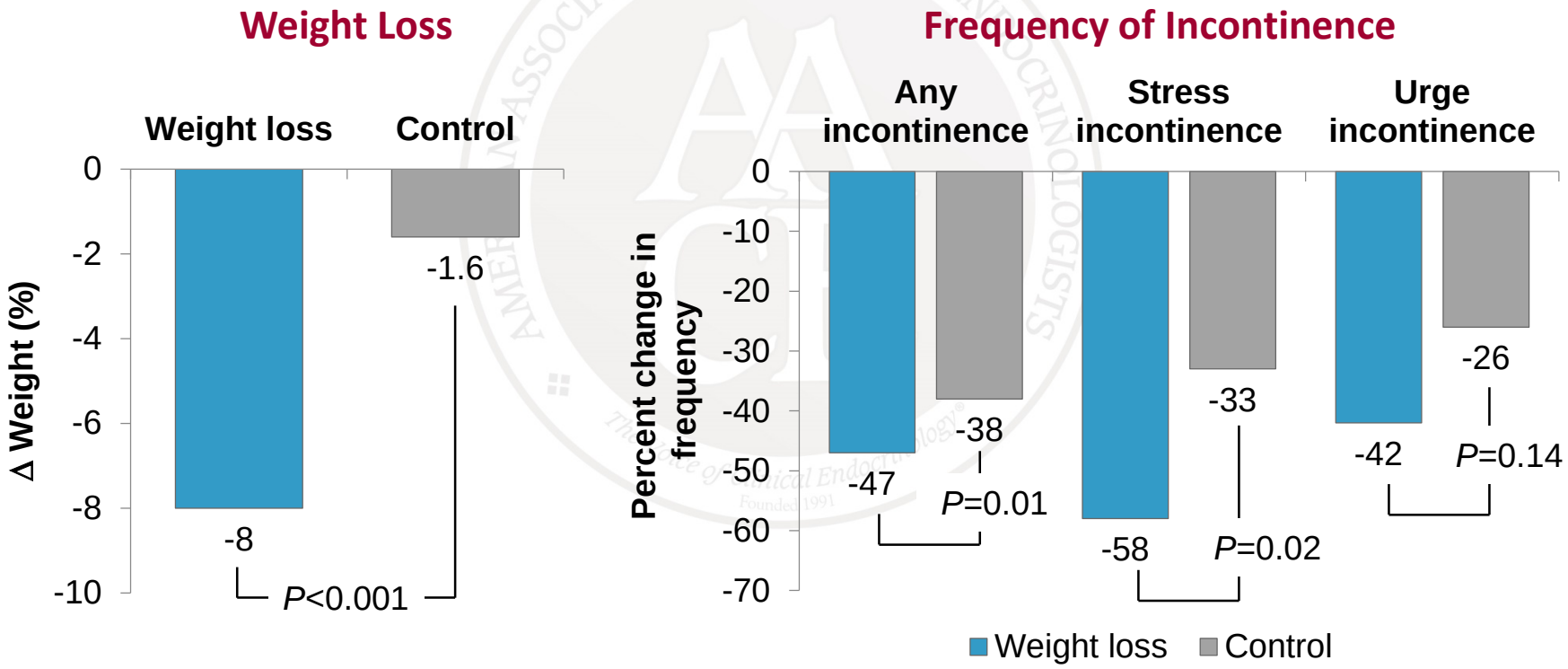


IL-6 = interleukin 6.

Messier SP, et al. *JAMA*. 2013;310:1263-1273.

Effect of Weight Loss on Urinary Incontinence in Women

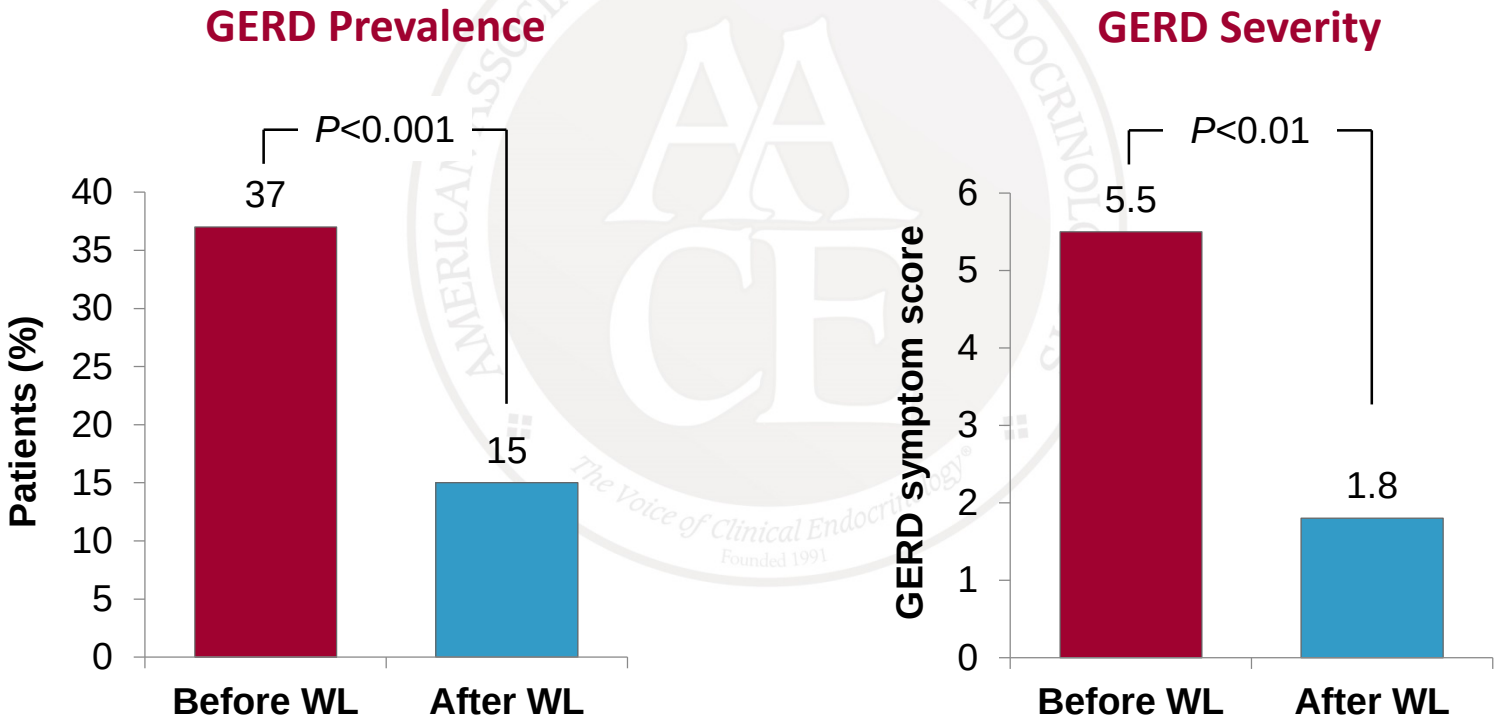
6-Month Randomized, Controlled Weight Loss Study (N=338)



Subak LL, et al. *N Engl J Med*. 2009;360:481-490.

Effect of Weight Loss on Gastroesophageal Reflux Disease

6-Month Prospective Observational Weight Loss Study
(N=332; mean WL: 13 ±7.7 kg)



GERD = gastroesophageal reflux disease.

Singh M, et al. *Obesity*. 2013;21:284-290.

Organ-Specific, Hormonal, and Biomechanical Complications

Cancer

Obesity and Cancer

Increased Risks

- Obesity increases risk of the following cancers:
  - Colon
  - Endometrium
  - Postmenopausal breast
  - Kidney
  - Esophagus
  - Pancreas
  - Gallbladder
  - Liver
  - Hematological malignancies
- Obesity worsens prognosis and mortality risk

Mechanism

- Obesity increases levels of leptin, IGF-1, and proinflammatory cytokines
  - These activate PI3K/Akt, which promotes cancer cell proliferation through mTOR
- Caloric restriction decreases levels of leptin, IGF-1, and proinflammatory cytokines
  - Signaling through AMPK is enhanced, promoting cancer cell apoptosis

AMPK = adenosine 5'-monophosphate–activated protein kinase; IGF-1 = insulin growth factor 1; mTOR = mammalian target of rapamycin; PI3K/Akt = phosphoinositide 3 kinase protein kinase B.

Vucenik I, Stains JP. *Ann NY Acad Sci.* 2012;1271:37-43.

Summary

- Numerous organ-specific and mechanical complications accompany obesity
  - Gallbladder disease
  - Sex hormone–related disorders
    - Polycystic ovary disease
    - Female infertility and male hypogonadism
  - Pulmonary disorders
    - Obstructive sleep apnea
    - Asthma/reactive airway disease
  - Biomechanical disorders
    - Osteoarthritis
    - Urinary stress incontinence
    - Gastroesophageal reflux disease
- Weight loss ameliorates all of these conditions