OBESITY MANAGEMENT IN PRIMARY CARE TRAINING AND CERTIFICATE PROGRAM

Obesity is a Complex Disease: Scope and Pathophysiology

Christine Kessler MN, CNS, ANP-BC, BC-ADM, CDCT, FAANP
Founder, Nurse Practitioner Metabolic Medicine Associates

AAPA THE OBESITY SOCIETY NACE

1

Disclosure Slide

- **NovoNordisk:** advisory board for type 2 diabetes and speaker for obesity
- **Clarion Brands:** research consultant for probiotic use with antibiotics
- **Acella Pharmaceuticals:** speaker for desiccated thyroid extract

2

Objectives

Accept	Accept obesity as a chronic disease based on the pathophysiology and impact on organ function.
Describe	Describe appetite control and energy balance regulation and the dysregulation that occurs in obesity.
Discuss	Discuss the multiple determinants of the development of obesity.
Explain	Explain the challenges underlying weight regain and metabolic adaptation.

3

What is obesity?

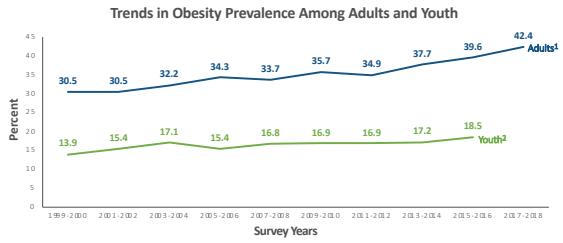
Image used with permission from Obesity Action Coalition

- Obesity is a **chronic**, **progressive**, **relapsing** disease that is associated with numerous complications, morbidities, and heightened mortality risk.

There is NO cure.

4

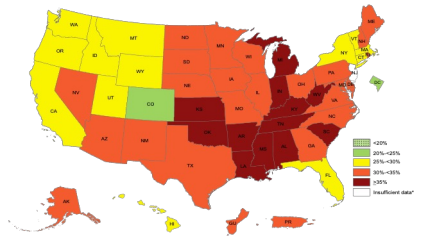
Obesity Rates Continue to Increase



1. Centers for Disease Control and Prevention. Accessed October 5, 2020. https://www.cdc.gov/nchs/products/databriefs/db360.htm. 2. Centers for Disease Control and Prevention. Accessed October 2, 2020. https://www.cdc.gov/nchs/data/databriefs/db288_table.pdf#5.

5

Prevalence*of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2019



Sample size <50, the relative standard error (dividing the standard error by the prevalence) ≥30%, or no data in a specific year.

*Prevalence estimates reflect Behavioral Risk Factor Surveillance System (BRFSS) methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011. Centers for Disease Control and Prevention. Accessed October 2, 2020. https://www.cdc.gov/obesity/data/prevalence-maps.html#overall.

6

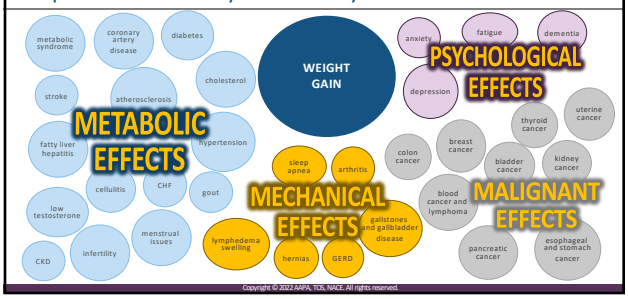
Classification of Overweight and Obesity by BMI and WC and Associated Disease Risk*

	BMI (kg/m²)	Disease Risk* (Relative to Normal Weight and WC†)	
		Men ≤ 40 in Women ≤ 35 in	> 40 in > 35 in
Underweight	<18.5	–	–
Normal	18.5-24.9	–	–
Overweight	25-29.9	Increased	High
Class 1 Obesity	30-34.9	High	Very High
Class 2 Obesity	35-39.9	Very High	Very High
Class 3 Obesity	≥ 40	Extremely High	Extremely High

*Disease risk for type 2 diabetes (T2DM), hypertension, and cardiovascular disease. †Increased WC can also be a marker for increased risk even in persons of normal weight.
BMI, body mass index; WC, waist circumference.
National Heart, Lung, and Blood Institute. Accessed October 2, 2020. https://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf.

7

Impact of Pre-obesity and Obesity on Health



8

The Cause of Obesity and Overweight is Simple…

… but is it *really* that simple?

9

How is obesity as a disease described?

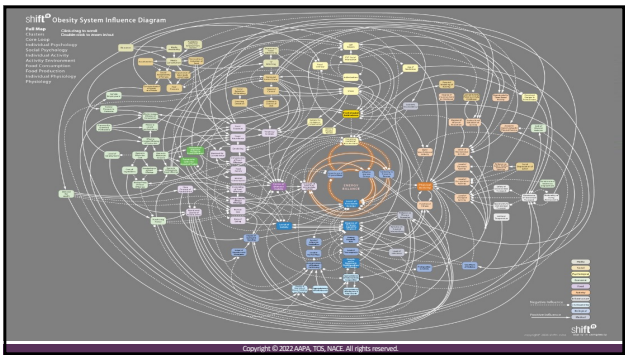
A. Multifactorial
B. Systemic
C. Metabolic
D. Relapsing
E. All of the above

10

How is obesity as a disease described?

A. Multifactorial
B. Systemic
C. Metabolic
D. Relapsing
E. All of the above

11



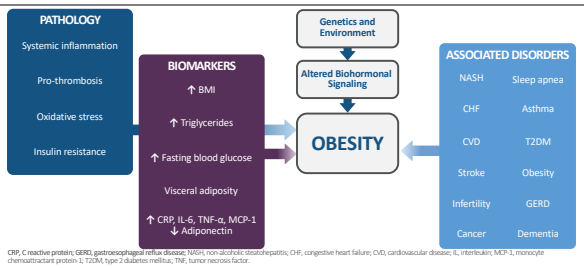
12

Obesity Risk is Complex and Multifactorial

Genetics and environmental influences can lead to altered biohormonal signaling, creating appetite and energy dysregulation that increases obesity risk

13

Obesity is a Systemic Inflammatory, Metabolic Disorder



CRP, C reactive protein; GERD, gastroesophageal reflux disease; NASH, non-alcoholic steatohepatitis; CHF, congestive heart failure; CVD, cardiovascular disease; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; T2DM, type 2 diabetes mellitus; TNF, tumor necrosis factor.

Adapted from: Mendrick D, et al. *Toxicol Sci.* 2018;162(1):36-42.

14

What About Metabolically Healthy Obesity (MHO)?[1-2]

MHO represents a subgroup of people with obesity who do not exhibit overt cardiometabolic abnormalities

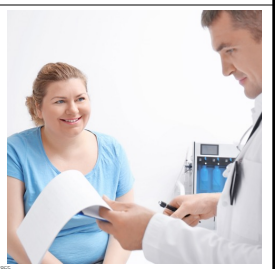
No standard definition of MHO but proposed criteria include:

- BMI ≥ 30 kg/m², TG < 150 mg/dL, HDL > 40 mg/dL (men)/ > 50 mg/dL (women), BP < 130/85 mm/Hg, FBG < 100 mg/dL
- Not on medications for the above conditions

Age- and gender-dependent prevalence approximately 10%-30%

Characterized by lower visceral fat but higher leg subcutaneous fat, lower inflammatory markers, greater insulin sensitivity, and better cardiopulmonary fitness

Believed to be a transient obesity phenotype that still represents a long-term risk for obesity-related morbidities (50% within 12 years)



BP, blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; TG, triglycerides.

1. Blüher M, et al. *Endocrine Reviews.* 2020;41(3):405-420. 2. Mongraw C, et al. *J Am Coll Cardiol.* 2018;71(17):1857-1865.

15

Genetic and Epigenetic Influences on Obesity Risk

16

About how many genes are known to play a role in obesity and overweight?

A. Approximately 30
B. Between 30 and 50
C. Between 60 and 80
D. Over 100

17

About how many genes are known to play a role in obesity and overweight?

A. Approximately 30
B. Between 30 and 50
C. Between 60 and 80
D. Over 100

18

Selected Genetic Determinants of Obesity from Genome-wide Association Studies (well over 100 known)

Gene	Tissue expressed	Gene product	Role in energy balance
MC4R	Adipocyte, hypothalamus, liver	Melanocortin 4 receptor	Appetite stimulation; monogenic cause of obesity
ADRB3	Visceral adipose tissue	β3-adrenergic receptor	Regulates lipolysis
PCSK1	Neuroendocrine cells (brain, pituitary, and adrenal glands)	Proprotein convertase 1	Conversion of hormones (including insulin) into metabolically active forms
BDNF	Hypothalamus	Brain-derived neurotrophic factor	Appetite stimulation; regulated by MC4R signaling and nutritional state
LCT	Intestinal epithelial cells	Lactase	Digestion of lactose
MTNR1B	Nearly ubiquitous	Melantonin receptor 1B	Regulation of circadian rhythms
TLR4	Adipocyte, macrophage	Toll-like receptor 4	Lipolysis, inflammatory reactions
ENPP1	Nearly ubiquitous	Ecotnucleotide pyrophosphatase/ phosphodiesterase 1	Inhibits tyrosine kinase activity of the insulin receptor, downregulating insulin signaling and decreasing insulin sensitivity
FGFR1	Adipose, hypothalamus	Fibroblast growth factor receptor 1	Hypothalamic regulation of food intake and physical activity
LEP, LEPR	Adipocyte	Leptin, leptin receptor	Appetite inhibition

den Hoed M, Loos RJF. In: Bray GA, Bouchard C, eds. *Handbook of Obesity*. 3rd ed. Boca Raton, FL: CRC Press; 2014:105-119.

19

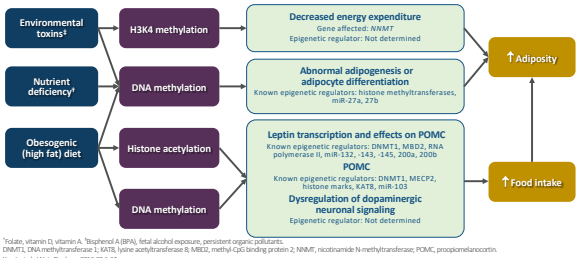
Summary of Genetic Obesity Risk Data

- DNA is **not** destiny
- Those with the *FTO* gene variant are 67% more likely to develop obesity
  - But they have a 27% greater ability to achieve weight loss with regular exercise
- Approximately 43% of Americans have a high polygenic risk for obesity
  - But this genetic risk does not guarantee obesity
  - 16% - 20% of those with very high polygenic obesity risk scores do not suffer from obesity
  - However, high polygenic obesity risk may make it harder to lose unwanted weight
- There are also rare single gene (monogenic) variants that greatly increase obesity, especially in childhood, and make it nearly impossible to lose weight

FTO, fat mass and obesity-associated.
Thaker VV, et al. *Adolesc Med State Art Rev*. 2017;28(2):379-405.

20

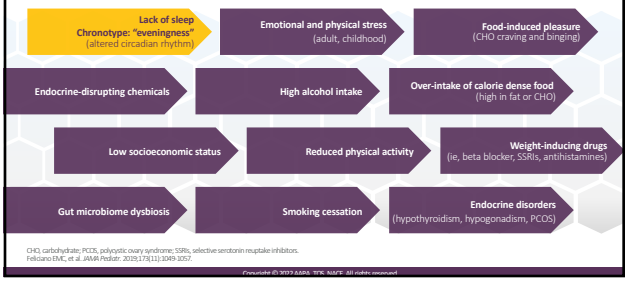
Mechanisms of Epigenetic Regulation



[2]Folate, vitamin D, vitamin A. [3]Bisphenol A (BPA), fetal alcohol exposure, persistent organic pollutants.
DNMT1, DNA methyltransferase 1; KAT8, lysine acetyltransferase 8; MBD2, methyl-CpG binding protein 2; NNMT, nicotinamide N-methyltransferase; POMC, proopiomelanocortin.
Xue J, et al. *J Nutr Biochem*. 2016;30:1-13.

21

Examples of Environmental Factors That May Influence Epigenetics



CHO, carbohydrate; PCOS, polycystic ovary syndrome; SSRIs, selective serotonin reuptake inhibitors.
Feliciano EMC, et al. *JAMA Pediatr.* 2019;173(11):1049-1057.

22

Physiology of Adipose Tissue

23

White Adipose Tissue (WAT)

Main form of adipose tissue

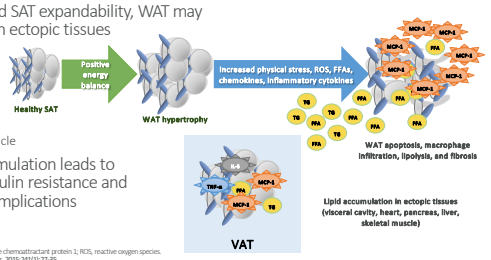
- Important *endocrine* organ that interacts with most other body organs
- Stores energy in the form of triglycerides
- An individual's fat mass is genetically set and maintained
- Normally found in subcutaneous adipose tissue (SAT) but can be found in ectopic locations (visceral and muscle)
- White adipose tissue composed of:
  - ~50% adipocytes
  - ~50% other cells
    - Stem/precursor cells
    - Preadipocytes
    - Vascular, neural, and immune cells
    - Leukocytes

Gustafson B, Smith U. *Atherosclerosis.* 2015;241(1):27-35.

24

Ectopic White Adipose Tissue and Consequences of Expansion

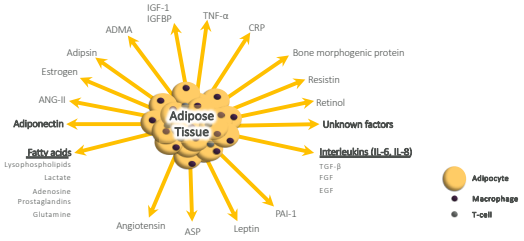
- Due to limited SAT expandability, WAT may accumulate in ectopic tissues
  - Viscera
  - Heart
  - Liver
  - Pancreas
  - Omentum
  - Skeletal muscle
- Ectopic accumulation leads to increased insulin resistance and metabolic complications



FFA, free fatty acid; MCP-1, monocyte chemoattractant protein 1; ROS, reactive oxygen species.
Gustafson B, Smith U. *Atherosclerosis*. 2015;241(1):27-35.

25

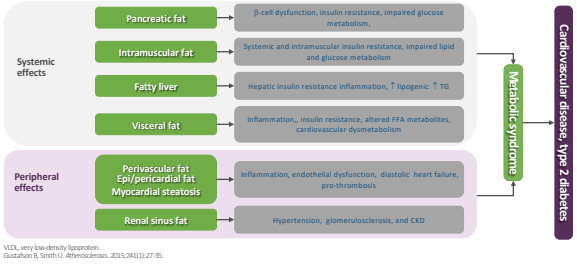
Visceral Adipose Tissue (VAT) Secretes Hormones and Inflammatory Factors



ADMA, asymmetric dimethyl-arginine; ANG-II, angiotensin II; ASP, acylation-stimulating protein; EGF, epidermal growth factor; FGF, fibroblast growth factor; IGF-1, insulin-like growth factor 1; IGFBP, insulin-like growth factor binding protein; PAI-1, plasminogen activator inhibitor 1; TGF-β, transforming growth factor β.
Itoh M, et al. *Int J Inflam*. 2011;2011:720926. Dixit VD. *J Leukoc Biol*. 2008;84(4):882-892.

26

Ectopic Fat Deposits Associated With Metabolic Disorders

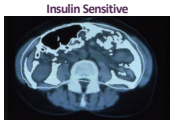


VLDL, very low-density lipoprotein.
Gustafson B, Smith U. *Atherosclerosis*. 2015;241(1):27-35.

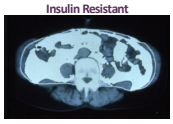
27

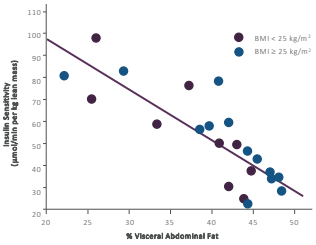
Association Between Visceral Fat and Insulin Resistance

Insulin Sensitive



Insulin Resistant





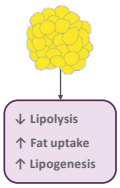
Computed tomography scans courtesy of Wilfred Y. Fujimoto, MD.
Carey DG, et al. *Diabetes.* 1996;45(5):633-638.

28

How Does Insulin Affect Body Weight?

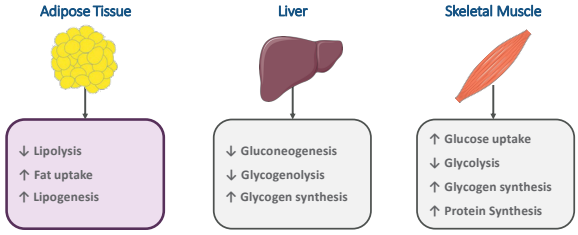
Insulin promotes fat storage (lipogenesis) and inhibits fat burning (lipolysis)

Food and drink will stimulate an insulin response to varying degrees, based on the content of what is ingested



29

Biological Effects of Insulin



Information from Murray RK, et al. *Harper's Illustrated Biochemistry.* 26th ed. New York, NY: Lange Medical Books/McGraw-Hill; 2003.

30

Hormones and Energy Balance

- Insulin is a hormone released from the pancreatic beta cells that signals to the brain the status of peripheral energy stores
- Acute changes in energy status are reflected in insulin levels:

Insulin increases during positive energy balance, such as meals

Insulin decreases during negative energy balance, such as fasting

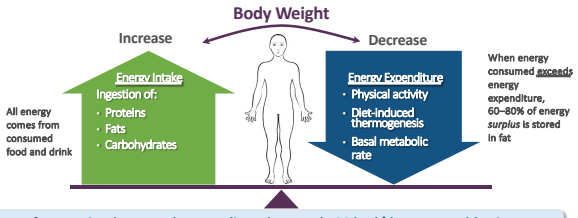
Bagdade JD, et al. *J Clin Invest*. 1967;46(10):1549-1557. Polonsky KS, et al. *J Clin Invest*. 1988;81(2):442-448.

31

Energy Metabolism

32

Energy Homeostasis

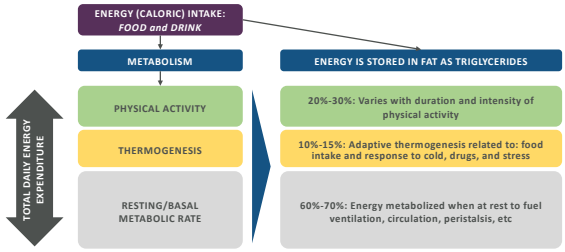


If energy intake exceeds expenditure by merely 20 kcal/day, one could gain approximately 1 kg of fat per year

Ouwaada SM, et al. *Metab Clin Exp*. 2019;92:26-36.

33

Energy Balance Metabolism



von Loeffelholz C, Birkenfeld A. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279077/.

34

Physiology of Appetite Regulation

35

Where does central regulation of weight occur?

A. The hypothalamus
B. The thalamus
C. The pancreas
D. The gut

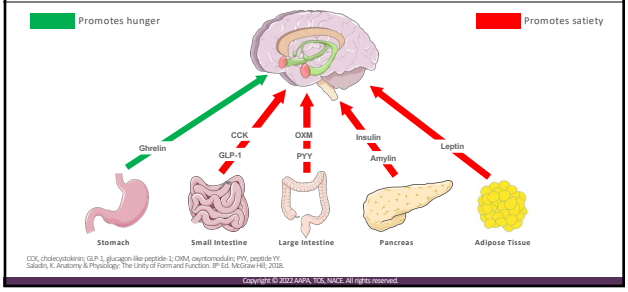
36

Where does central regulation of weight occur?

A. The hypothalamus
B. The thalamus
C. The pancreas
D. The gut

37

The Hypothalamus Centrally Regulates Weight but is Influenced by Peripheral Signals



CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PYY, peptide YY.
Saladin, K. Anatomy & Physiology: The Unity of Form and Function. 8th Ed. McGraw Hill; 2018.

38

The Hypothalamus Centrally Regulates Weight but is Influenced by Peripheral Signals

NPY and AgRP Neurons:

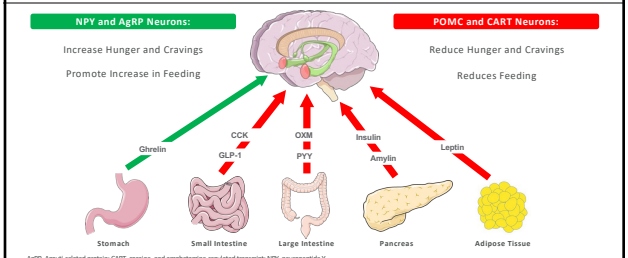
Increase Hunger and Cravings

Promote Increase in Feeding

POMC and CART Neurons:

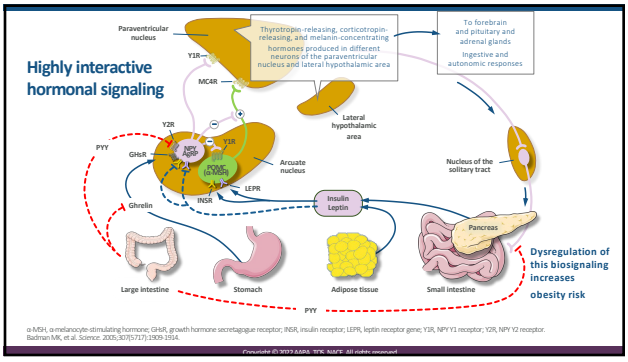
Reduce Hunger and Cravings

Reduces Feeding



AgRP, Agouti-related protein; CART, cocaine- and amphetamine-regulated transcript; NPY, neuropeptide Y.
Saladin, K. Anatomy & Physiology: The Unity of Form and Function. 8th Ed. McGraw Hill; 2018.

39

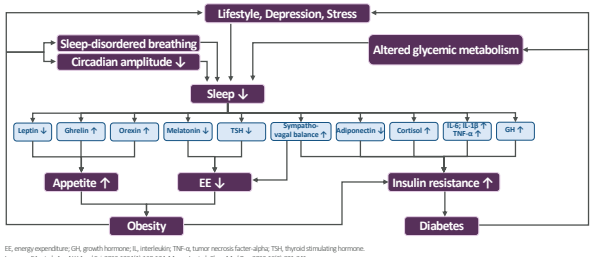


40

Impact of Sleep and Stress

41

Influences of Sleep Disorders on Appetite and Obesity (and Diabetes)



EE, energy expenditure; GH, growth hormone; IL, interleukin; TNF-α, tumor necrosis factor alpha; TSH, thyroid stimulating hormone.
Lucassen EA, et al. *Ann N Y Acad Sci*. 2012;1264(1):110-134. Magee L, et al. *Sleep Med Rev*. 2012;16(3):231-241.

42

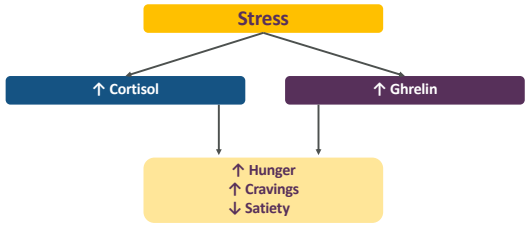
Chronotype and Obesity Risk

- Chronotype ("eveningness" vs "morningness") influences several physiologic and metabolic processes
- An evening tendency is related to higher BMI and obesity risk
- The relationship between chronotype and BMI appears to be mediated by inflammation levels
  - An evening tendency is associated with elevated inflammatory biomarkers (CRP, IL-6) and a greater cortisol stress response
  - Increased cortisol and inflammatory responses correlate with increased BMI
  - **The greater the cortisol response, the greater the obesity risk**
- An evening chronotype (and poor sleep) has been found to increase central adiposity and inflammatory biomarkers in adolescent girls (Project Viva Study)

Feliciano EMC, et al. *JAMA Pediatr.* 2019;173(11):1049-1057. de Punder K, et al. *Psychoneuroendocrinology.* 2019;109:104388.

43

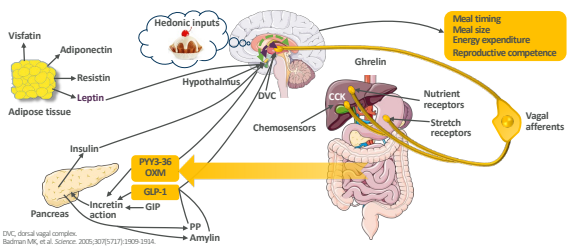
Effect of Stress on Hunger and Appetite



Kumar J, et al. *Appetite.* 2013;64:81-88.

44

Hormonal Signals From Gut, Pancreas, and Adipose Tissue to Brain Affects Food Intake

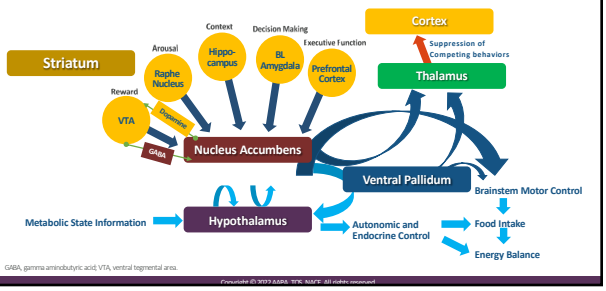


DVC, dorsal vagal complex.

Badman MK, et al. *Science.* 2005;307(5717):1909-1914.

45

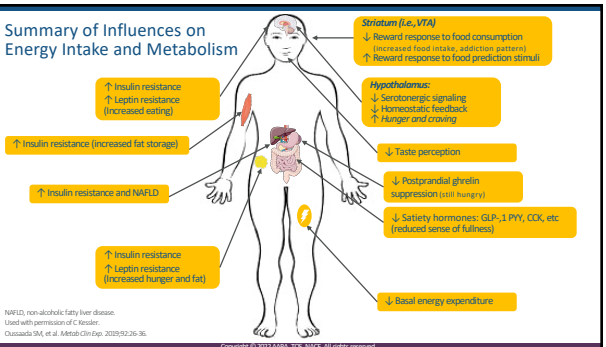
Satisfaction (Reward) Signaling and Impact on Food Craving



GABA, gamma aminobutyric acid; VTA, ventral tegmental area.

46

Summary of Influences on Energy Intake and Metabolism



NAFLD, non-alcoholic fatty liver disease.
Used with permission of C Kessler.
Oussaada SM, et al. *Metab Clin Exp.* 2019;92:26-36.

47

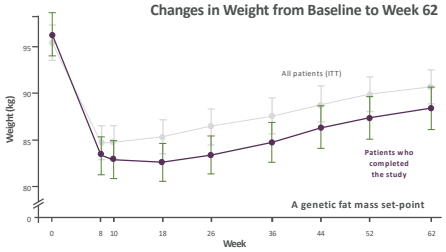
Many people who lose weight . . . regain

WHY?

Image used with permission from Obesity Canada

48

Metabolic Adaptation: What Happens When We Lose Weight?



Most people who lose weight regain within 1 year

ITT, intent to treat.
Sumithran P et al. *N Engl J Med.* 2011;365(17):1597-1604.

49

Obesity-Related Hormonal Regulation of Appetite and Energy Balance

Key Hormone Changes Associated with Weight Gain and Regain

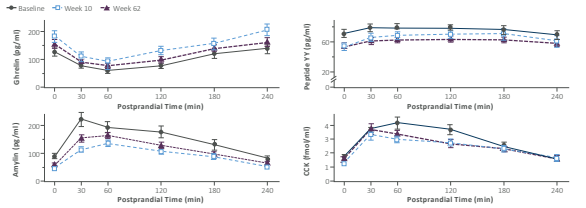
Hormone	Source	Normal function	Alteration
Cholecystokinin	Duodenum	Suppresses appetite	Levels decrease during dieting and weight reduction
Glucose-dependent insulinotropic polypeptide	Duodenum, jejunum	Energy storage	Levels increase during dieting and weight reduction
Ghrelin	Gastric fundus	Stimulates appetite, particularly for high-fat, high-sugar foods	Levels increase during dieting and weight reduction
Glucagon-like peptide 1	Ileum	Suppresses appetite and increase satiety	Decreased functionality
Insulin	Pancreas	Regulates energy balance Signals satiety to brain	Insulin resistance in obesity Reduced insulin levels after dieting
Leptin	Adipocytes	Regulates energy balance Suppresses appetite	Levels decrease during weight reduction
Peptide YY	Distal small intestine	Suppresses appetite	Levels decreased in obesity

Sumithran P, et al. *Clin Sci (Lond).* 2013;124:231-241.

50

As We Lose Weight, Hunger Hormones Go Up and Satiety Hormones Go Down! (*Metabolic Adaptation*)

Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and CCK at Baseline, 10 weeks, and 62 Weeks

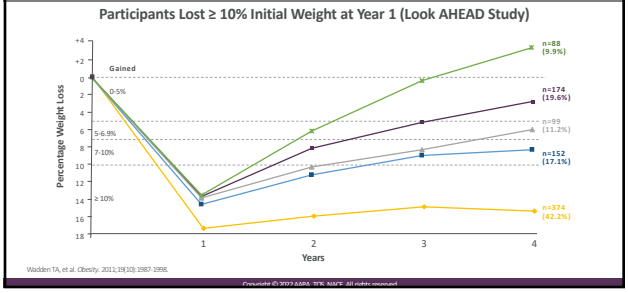


Hunger hormones increase and satiety hormones decrease

Sumithran P et al. *N Engl J Med.* 2011;365(17):1597-1604.

51

Four-year Weight-loss Trajectories of 887 Intensive Lifestyle Intervention Participants



Wadden TA, et al. Obesity. 2011;19(10):1987-1998.

52

Metabolic Adaptation and Energy

As We Lose Weight, Metabolism Slows Down!

Weight loss may trigger a reduction in basal (resting) metabolic rate by **more than 15%** beyond what is predicted after adjustment for changes in body composition.

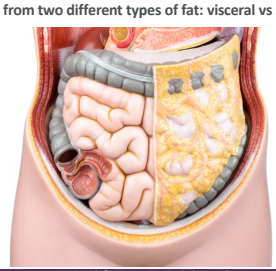
There is a disproportionate change in energy expenditure not only during, but also well beyond the period of weight change.

Adapted from: Lam YY, Ravussin E. *Mol Metab.* 2016;5(11):1057-1071.

53

Benefits of 5-10% Weight Reduction

Weight loss from two different types of fat: visceral vs subcutaneous



54

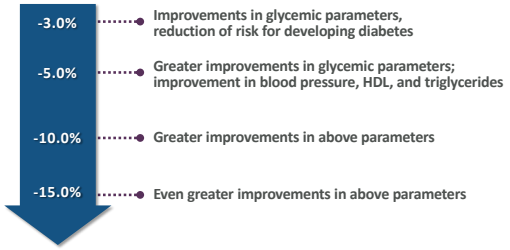
Benefits of 5-10% Weight Reduction

Condition	Amount of Weight Loss	Benefits
Blood Pressure	5%	↓ systolic by 5 mm/Hg ↓ diastolic by 5 mm/Hg
Cholesterol	5%	↑ HDL by 5 mg/dL ↓ Triglycerides by 40 mg/dL
Pre-Diabetes	5%	↓ T2DM by 50%
Diabetes	5%	↓ A1c by 0.5%
Sleep Apnea	10%	↓ apnea episodes by up to 50%
Arthritis	5-10%	↓ mechanical force off knee by up to 7x the weight loss
NASH	10%	↓ liver inflammation and necrosis but not fibrosis

Wing RR, et al. *Diabetes Care*. 2011;34(7):1481-1486.

55

Meaningful Weight Loss is the Goal



Jensen MD, et al. *J Am Coll Cardiol*. 2014;63(25 Pt B):2985-3023.

56

Conclusions: Is Obesity a Disease?

Old Paradigm	New Paradigm
No. But it's associated with diseases. It's a risk factor.	**Yes.** It is an impairment of normal functioning of energy balance regulation; that impairment produces morbidity.
No. There are people with BMI ≥ 30 kg/m² who are perfectly healthy.	**Yes.** But let's not use BMI to name call. Let's use it as a screening tool to identify risk.
No. It is something that anyone could change with better habits if they tried. It must be a personal choice.	**Yes.** Inherited and environmental factors strongly influence risk for overweight. And once weight is gained, physiology resists loss.

Used with permission from Robert Kushner, MD.

57

Conclusions: What Causes Obesity?

Old Paradigm	New Paradigm
Bad lifestyle choices.	Genetic susceptibility aggravated by an environment structured to low levels of activity and ready access to energy dense, highly palatable foods.
Lack of education about healthy choices.	Stress, lack of sleep, and hypoglycemia all inhibit higher cortical restraint to reward eating.
Not enough willpower.	Hypothalamic gliosis and physiology of reduced obesity (disproportionate ↓ in REE, leptin, PYY, and CCK and ↑ in ghrelin) thwart weight loss and promote weight gain.

REE, resting energy expenditure.
Used with permission from Robert Kushner, MD.

58

Conclusions: Pathogenesis of Weight Regain

Old Paradigm	New Paradigm
We will reduce the patient and the patient will be cured.	Obesity is a chronic, relapsing condition; once overweight, metabolic challenges persist.
Weight regain occurs because patients resume bad habits.	The reduced obese state often elicits a metabolic adaptation causing a decrease in metabolic rate and increased appetite signals .
Patients could lose weight and maintain lost weight if they had strong will power.	Weight loss maintenance requires special treatment approaches.

Used with permission from Robert Kushner, MD.

59

Conclusions: Thoughts on How Much Weight Loss Is Needed to Produce Health Benefits

Old Paradigm	New Paradigm
Everyone needs to reach an ideal body weight (in US, BMI < 25 kg/m^2; in South Asians, < 23 kg/m^2).	1. Modest weight loss can bring health benefits; more loss = more benefits. 2. Different tissues respond differently to gradations in weight loss amount.
Modest weight loss is futile in people with extreme obesity.	Even in patients with BMI > 40 kg/m^2, modest weight loss produces some improvements.

Used with permission from Robert Kushner, MD.

60

Understanding the Chronic Disease of Obesity Is an Important Step Toward Success!

61