JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 71, NO. 1, 2018

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
https://doi.org/10.1016/j.jacc.2017.11.011

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Obesity

Pathophysiology and Management

Kishore M. Gadde, MD, Corby K. Martin, PhD, Hans-Rudolf Berthoud, PhD, Steven B. Heymsfield, MD

ABSTRACT

Obesity continues to be among the top health concerns across the globe. Despite our failure to contain the high prevalence of obesity, we now have a better understanding of its pathophysiology, and how excess adiposity leads to type 2 diabetes, hypertension, and cardiovascular disease. Lifestyle modification is recommended as the cornerstone of obesity management, but many patients do not achieve long-lasting benefits due to difficulty with adherence as well as physiological and neurohormonal adaptation of the body in response to weight loss. Fortunately, 5 drug therapies—orlistat, lorcaserin, liraglutide, phentermine/topiramate, and naltrexone/bupropion—are available for long-term weight management. Additionally, several medical devices are available for short-term and long-term use. Bariatric surgery yields substantial and sustained weight loss with resolution of type 2 diabetes, although due to the high cost and a small risk of serious complications, it is generally recommended for patients with severe obesity. Benefit-to-risk balance should guide treatment decisions. (J Am Coll Cardiol 2018;71:69–84) © 2018 by the American College of Cardiology Foundation.

Obesity, which is broadly defined as excess body weight for a given height, remains a continuing global health concern, as it is associated with increased risk of numerous chronic diseases including type 2 diabetes (T2D), hypertension, and cardiovascular disease (CVD). Body mass index (BMI) (weight in kg/height in m^2), the most widely used formula to define overweight (BMI 25 to 29.9 kg/m^2) and obesity (BMI ≥30 kg/m^2), while not being a true measure of adiposity, is simple to use in health screenings and epidemiological surveys. A recent analysis of data from 195 countries revealed that the prevalence of obesity has doubled in more than 70 countries since 1980, and over 600 million adults were obese in 2015, with high BMI accounting for 4 million deaths globally (1). The pathogenesis of obesity is complex, with environmental, sociocultural, physiological, medical, behavioral, genetic, epigenetic, and numerous other factors contributing to causation as well as persistence (2).

PATHOPHYSIOLOGY

Controlling energy intake and energy expenditure are the main mechanisms by which energy balance is achieved. For this basic energetic equation, it is true that a calorie really is a calorie, and all calories are equal. However, we realize that not all calories are equal when we look beyond this purely energetic consideration and consider the pathogenesis of obesity-related comorbidities. Therefore, a proper explanation of the pathophysiology of obesity includes

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana. Dr. Gadde is an advisor to AstraZeneca with payments made to his employer, Pennington Biomedical Research Center; has received research support from the National Institutes of Health (NIH) and AstraZeneca; and has received speaking honoraria from the American Diabetes Association. Dr. Martin has served as an advisor for ACAP Health, Zafgen, Gila Therapeutics, Weight Watchers, Florida Hospital and Kitchry; has received research funding from the NIH, Centers for Disease Control, U.S. Department of Agriculture, Ohio State University, Elizabeth Blackwell Institute for Health Research, Patient-Centered Outcomes Research Institute, Egg Board, University of Pennsylvania, Louisiana LIFT Fund, Weight Watchers, and Regents of Georgia State University, and Access Business Group International; and has received royalties from his institution licensing smartphone-based technology he invented. Dr. Berthoud has received research funding from the NIH. Dr. Heymsfield has received fees for serving on advisory boards from Janssen Pharmaceuticals, Tanita, Merck, and Medifast.

Manuscript received July 22, 2017; revised manuscript received October 3, 2017, accepted November 6, 2017.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CI = confidence interval

CVD = cardiovascular disease

CVOT = cardiovascular outcomes trial

FDA = Food and Drug Administration

HF = heart failure

HgA_{1c} = glycosylated hemoglobin

ILI = intensive lifestyle intervention

LAGB = laparoscopic adjustable gastric band

LV = left ventricular

MACE = major adverse cardiovascular events

MRI = magnetic resonance imaging

NB = naltrexone/bupropion

PHEN/TPM = phentermine/topiramate

RCT = randomized controlled trial

RYGB = Roux-en-Y gastric bypass

SG = sleeve gastrectomy

T2D = type 2 diabetes

2 parallel discussions: 1 from an energetic and 1 from a nutritional standpoint. Here, we focus mainly on the former, due in large part because there is considerable consensus for the mechanisms of energy balance regulation, whereas there is confusion and controversy regarding optimal nutrient composition (3,4). The distinction between the causes and consequences of obesity must be given due consideration, as also the importance of understanding obesity-independent and obesity-dependent pathophysiology of comorbidities including CVD.

On the basis of observations that individual adult body weight is remarkably stable and refractory to short-term experimental up or down perturbations under constant environmental conditions, most scientists agree that body weight or adiposity is actively regulated or defended (5). New insights suggest that the elevated body weight/adiposity in many obese subjects is defended just as it is in normal weight subjects (6), supporting the notion that obesity is a disease, thus shifting the blame from the person to the physiology.

Genome-wide association study-based data suggest a genetic predisposition for obesity with identification of more than 140 genetic chromosomal regions related to obesity (7). Gene expression related to BMI and general adiposity is highly enriched in the central nervous system (8). However, only a few genes with a large effect size on BMI have yet been identified. These are the genes encoding components of leptin and melanocortin signaling, as well as paternally expressed genes along a specific region of chromosome 15 responsible for Prader-Willi syndrome (9). In contrast to such monogenetic cases, common obesity is thought to be associated with a large number of genes with small effect sizes.

A widely held view is that obesity results from an interaction between environment/lifestyle and genetic susceptibility. Several hypotheses have been put forward to explain the existence of obesity susceptibility genes. The "thrifty" gene hypothesis posits that genes promoting energy intake and high fuel efficiency were selected over genes promoting energy-guzzling during human evolution (10). The "drifty" gene hypothesis argues that the evolutionary selection pressure for genes keeping body weight/adiposity to a minimum relaxed when humans invented weapons and fire about 2 million years ago, and thus were no longer threatened by predators, with the consequence of a random drift of genes allowing increased adiposity (11).

The early origins of adult disease hypothesis suggests that obesity can develop in offspring from mothers exposed to metabolic hardship such as undernutrition, obesity, and diabetes (12). One of the molecular mechanisms responsible for early-life metabolic programming is epigenetic modification of genes through methylation, histone modifications, chromatin remodeling, and noncoding RNA alterations (13). Importantly, such epigenetically determined increased risk for adult obesity can be transmitted to future generations, further accelerating the obesity epidemic. Thus, finding the tools and therapies to break the vicious circle of epigenetic programming is an important target of obesity research.

Given the disproportionally high expression of obesity-associated genes and epigenetic modifications in the central nervous system, it is highly likely that obesity genes act, not only within the hypothalamic homeostatic regulator of energy balance, but also within neural circuits that are involved in interactions with an obesogenic environment, including circuits underlying reward-based decision making, learning and memory, delayed discounting, and spatial orientation.

CONTROLLING FOOD INTAKE IN AN ENVIRONMENT OF PLENTY

Although the brain primarily regulates food intake as a behavior, it relies on information from the rest of the body and from the environment to make the decision to eat or not to eat. Well over 50 years ago, seminal studies established the hypothalamus as a key hub for the detection of hunger and organization of eating behavior (14). Since then, the importance of the hypothalamus has been confirmed, with much detail added to its functional and chemical anatomy (15). In addition, the importance of crosstalk (**Figure 1**) between the hypothalamus and other brain regions, as well as with the periphery, has been recognized (16).

A key function of the basomedial hypothalamus is to detect shortages in nutrient supply, both short term and long term, and translate them into behavior. To this end, separate groups of chemically distinct neurons (agouti-related peptide/neuropeptide Y [AGRP/NPY] and proopiomelanocortin/cocaine and amphetamine regulated transcript [POMC/CART]) are sensitive to circulating metabolites and hormones signaling availability of energy, such as leptin, ghrelin, insulin, and glucose, in addition to neural signals reflecting the nutritional status of the gut conveyed