Biology of obesity and weight regain: Implications for clinical practice

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Adipogenesis; obesity pathophysiology; weight regain; obesity recidivism; obesity relapse.

Abstract

Background and purpose: Weight loss is recommended as first-line therapy for many chronic illnesses, including obesity. Most patients who do successfully lose weight are unable to maintain their reduced weight. Recent research findings are reviewed and synthesized to explain the biology of obesity, adaptation to weight loss, and weight regain.

Findings: Weight regain is a common consequence of successful weight loss. Current obesity management strategies fail to take into consideration the underlying genetic and environmental causes of obesity. Available treatment modalities create a negative energy balance that stimulates integrated, persistent neurologic, endocrine, muscle, and adipose tissue adaptation to restore body weight and fat mass, independent of lifestyle changes.

Implications for practice: Understanding the pathophysiology of obesity and weight loss alters nurse practitioners’ responsibilities in caring for patients with obesity. They are responsible for expanding assessment and intervention strategies and offering people with obesity realistic expectations for weight loss and regain. They are obligated to explain weight regain when it occurs to minimize patient frustration. Nurse practitioners have the opportunity to adopt new approaches to patient advocacy, especially in the areas of public policy to improve diagnostic tools and adjunctive therapy for people with obesity.

Introduction

Historically, obesity, or excess adipose tissue mass, has been conceptualized as a homogenous disease of individuals eating too much and exercising too little. Obesity management has focused on inducing the obese person to eat less and engage in more physical activity to achieve a more normal weight and body composition. The past four decades of basic and clinical research have demonstrated that obesity results from impaired energy regulation, and that efforts to promote weight loss through behavioral and surgical interventions create a negative energy balance, not a normalization of energy homeostasis. The negative energy balance in turn sets the stage for unintentional weight regain following successful weight loss. The genetic variability in predisposition to obesity and biological adaptation to weight loss have led MacLean, Blundell, Menella, and Batterham (2017) to call self-regulation of appetite and eating behavior “a daunting complexity.” Because this “daunting complexity” is fundamental to the clinical management of obesity, the purpose of this article is to describe the normal physiological processes regulating energy balance. Disruptions in energy regulation leading to the development of obesity will be discussed, and the physiological adaptations associated with weight loss and regain will be described, along with implications for clinical practice.

Definition and causes of obesity

Obesity is a chronic multifactorial disorder of excess lipid accumulation in adipose tissue and in ectopic sites such as in skeletal muscle and the liver. It is caused by the interaction of environmental factors and genetic predisposition, leading to a positive energy balance, in which fuel intake exceeds energy expenditure. Obesity is usually defined by a body mass index (BMI) greater than 30 kg/m² in adults, and in children as a BMI equal to or greater than the 95th percentile for sex and age.
Biology of obesity and weight regain

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(Ogden & Flegal, 2010). Environmental influences believed to contribute to obesity include easy availability of energy dense foods; sedentary lifestyle because of mechanization, automobiles, and electronic media; and parental nurturing and feeding practices (Campbell, 2016). While family, twin, and adoptee studies have demonstrated the heritability of obesity ranges between 35% and 90%, only a few monogenic causes of obesity have been identified, and little of the apparent heritability of obesity has actually been explained to date (Xia & Grant, 2013). Nevertheless, the body’s energy storage and utilization, adipose mass, and weight are biologically regulated by the interactions of orexigenic (appetite-stimulating) and anorexigenic (appetite-suppressing) pathways. These pathways are mediated by a range of factors including neuroendocrine signal transmission, adipocyte biology, skeletal muscle performance, and gut-derived signals.

The problem of weight regain after weight loss

Treatment of obesity relies on creating a negative energy balance through lifestyle changes, designed to decrease food intake and increase physical activity, combined with pharmacologic therapy, or bariatric surgery in some cases. A national survey revealed 63% of American adults had attempted to lose weight, averaging 5.3 weight loss episodes in their lifetimes (Saad, 2011). Estimated costs in the United States for weight-loss products, including fitness equipment, weight-loss services, medications, bariatric surgery, and diet foods, were U.S. $148.1 billion in 2014, and are projected to rise to $206.4 billion by 2019 (Research and Markets, 2015). Despite these high expenditures, weight regain frequently follows weight loss, and many people regain more weight than they initially lost.

The most recent obesity management guidelines (Jensen et al., 2014) do not define weight regain or successful weight maintenance. Previously, the National Heart Lung and Blood Institute defined successful weight loss as 10% of body weight, and weight maintenance was defined as a weight regain of <3 kg (6.6 pounds) in 2 years (National Heart, Lung, and Blood Institute, 1998). A recent poll of bariatric surgeons found no consistent definition of weight regain (Nedelcu, Khwaja, & Rogula, 2016). Because of the lack of consistency in measuring weight regain among authors and researchers, Stevens, Truesdale, McClain, and Cai (2006) proposed standardizing the definition of weight maintenance; taking into account normal weight fluctuations they defined weight maintenance for adults as a regain of less than 3% of their body weight nadir.

Weight-loss attempts often lead to higher weights in the long term. For example, a study in both monozygotic and dizygotic twins demonstrated that those with one or more episodes of intentional weight loss gained progressively more weight by age 25 years than their nondieting twin siblings (Pietilainen, Saarini, Kaprio, & Rissanen, 2012). In a longitudinal study, the odds of obesity were 1.9, 2.9, and 3.2 times higher for those who were on a diet once, more than once, and always in the previous year, compared with those who had not dieted (Siahpush et al., 2015). Studies also suggest that weight plateaus occur approximately 10 weeks to 6 months into weight-loss programs (Franz et al., 2007; Sumithran et al., 2011) and that one- to two-thirds of dieters regain more weight than was lost from the dietary intervention (Mann et al., 2007).

Bariatric surgery is the most effective and long-lasting means of weight loss, with weight loss at 1–2 years of 20–30 kg with surgery versus <5.5 kg with nonsurgical weight management (Colquitt, Pickett, Loveman, & Frampton, 2014). Surgical intervention also significantly decreases comorbidity factors including blood glucose levels, lipid profiles, and blood pressure. Even following bariatric surgery, however, individuals are confronted with the problem of weight regain after substantial weight loss. Studies estimate that a median of 20% of bariatric procedures fail because of weight gain or insufficient weight loss (Sheppard et al., 2013). A prospective study found that loss of excess weight from baseline was no longer significant 24 months after gastric bypass surgery, and that weight regain became significant within 48 months in approximately 50% of patients (Magro et al., 2008). Lifestyle factors including fitness, physical activity, and dietary intake at 2 years postoperatively were not predictive of weight regain at 6 years (Davidson, Adams, & Hunt, 2012), indicating that lifestyle modification may have limited effectiveness in controlling weight regain.

The finding that adult body weight remains relatively stable over long periods of time and that weight is readily recovered after voluntary weight loss have given rise to the “set-point theory” of obesity (Nisbett, 1972). This theory proposes that individual weight is maintained within a range of predetermined values which represents a state of equilibrium between energy storage and utilization. Maintaining weight within the narrow set-point range depends on the integration of feedback signals from the periphery to a central controller, which is able to modulate food intake and energy expenditure to correct body-weight deviations. Signals from adipose tissue, muscles, gastrointestinal tract, and other tissues relay information about the state of fuel intake, fuel storage, and energy expenditure, which are integrated in the central nervous system to regulate hunger, satiety, feeding behavior, and energy expenditure.

Many of the components of the feedback regulation of body weight and adiposity have been identified since the introduction of the set-point theory, and help to explain the challenges of maintaining weight loss. Genetic,
epigenetic, and environmental effects are thought to determine the set point for body weight, although the exact mechanisms for establishing the set point are poorly understood (Muller, Bosy-Westphal, & Heymsfield, 2010). The biological processes leading to obesity and adipose regain following successful weight loss will be described in the following sections.

**Development of excess adipose tissue**

Obesity is the accumulation of excess adipose tissue (fat mass), comprised primarily of adipocytes along with endothelial and neuronal cells and macrophages (Berry, Stenesen, Zeve, & Graff, 2013). Adipose tissue has important functions in the regulation of total body energy homeostasis, temperature, reproduction, glucose balance, and immunity. Adipocytes are derived from multipotent mesenchymal stem cells, which differentiate first to fibroblasts, then to preadipocytes, and finally to mature adipocytes. Peroxisome proliferator-activated receptor gamma (PPAR-γ) is required for adipocyte differentiation, and its activation is sufficient to induce adipocyte differentiation in fibroblasts. PPAR-γ expression is stimulated by numerous environmental factors that have been shown to lead to obesity or excess weight gain, including some antidiabetes medications (thiazolidinediones; TZDs) and human adenovirus-36 (Dubuisson et al., 2011).

A multitude of cellular and hormonal signals also promote different aspects in the progression of fibroblast to adipocyte maturation, including insulin, insulin-like growth factor-1, and glucocorticoids (Rosen & Spiegelman, 2000). Conversely, sympathetic nervous system (SNS) stimulation inhibits adipocyte proliferation. Nonselective beta-blockers such as the medication propranolol counter this suppression of adipocyte proliferation by the SNS, which explains why a prominent adverse side effect of propranolol is weight gain (Bartness, Liu, Shrestha, & Ryu, 2014; Penicaud & Lorsignol, 2013).

Adipose tissue expansion occurs through hypertrophy (increase of lipid volume within each adipocyte) or hyperplasia (increase in the number of adipocytes). Adipocyte hypertrophy allows for greater storage of triglycerides within each cell. Adipocyte size varies by location of fat tissue within the body, and fat-cell size can vary as much as 100% between adipose depots within an individual (Salans, Cushman, & Weismann, 1973). It is thought that when adipocytes within a particular region reach a critical volume through hypertrophy, adipocyte hyperplasia occurs to increase lipid storage capacity (Moreno-Navarrete & Fernandez-Real, 2012). Hager, Sjorstrom, Arvidsson, Bjorntorp, and Smith (1978) observed that prepubertal girls with obesity, treated with a dietary and physical activity weight-loss regimen, continued to increase their fat-cell number, even as they reduced their total body fat and adipocyte cell size.

Large adipocytes are less responsive to insulin, and evoke local and systemic inflammatory responses (Berry et al., 2013), leading to the undesirable metabolic effects of obesity and increased risk for insulin resistance, type 2 diabetes (T2D), nonalcoholic steatohepatitis, and coronary artery disease. Impaired activation of adipocyte hyperplasia has been found to result in ectopic fat distribution in liver, muscles, and pericardial area and is associated with increased cardiovascular and T2D risk (Gustafson & Smith, 2015).

**Types of adipocytes**

There are three types of adipocytes: white, brown, and beige. White adipocytes have a single large lipid droplet and few mitochondria. White adipose tissue is distributed primarily in the intra-abdominal visceral compartment (visceral adiposity) and in the gluteal and femoral regions (subcutaneous fat). White adipocytes function primarily to store lipid and to release fatty acids when they are needed for cellular functions, including the production of adenosine triphosphate (ATP) for cellular energy.

Binding of epinephrine and norepinephrine to beta-adrenergic receptors on white adipocytes initiates the release of fatty acids for fuel (Bartness et al., 2014; Lieberman & Lichtenberg, 2014). Various genetic polymorphisms in the beta-adrenergic receptors on adipocytes impair catecholamine (epinephrine and norepinephrine) stimulated release of fatty acids. These polymorphisms increase the risk of developing obesity (Liu, Mo, Huang, & Zhou, 2007; Zhang, Wu, & Yu, 2014), and convey resistance to a weight-loss program of diet and exercise (Loos, Vimaleswaran, & Wareham, 2008; Masuo & Lambert, 2011). In contrast, selective alpha₂-adrenergic receptor activation suppresses lipolysis (Penicaud & Lorsignol, 2013). Therefore, the net effect of catecholamine stimulation of white adipose tissue is dependent on the number of alpha- and beta-adrenergic receptors on adipocytes and their affinity for catecholamines (Lafontan, 2008).

Brown adipocytes are found in adipose tissue located primarily in the cervical and subclavicular regions. Brown adipocytes contain multiple small lipid droplets. These cells are rich in mitochondria that dissipate energy, and are primarily involved in nonshivering thermogenesis for heat production (Sidossis & Kajimura, 2015). Brown adipose tissue is prominent in small animals, and until recently was thought to exist in human beings only in infants and young children. However, metabolically active brown adipose depots have been identified in adults, and can be activated with exposure to mild cold (Virtanen et al., 2009). Adults with obesity are deficient in brown adipose
tissue compared to adults with normal weight. Genetic variants in alpha-ketoglutarate-dependent dioxygenase, better known as the fat mass and obesity-associated (FTO) protein gene, have been linked to lower brown adipose tissue in human subjects (Claussnitzer et al., 2015).

Beige or brite adipocytes are brown-like adipocytes, with many mitochondria and thermogenic capacity, interspersed within subcutaneous white adipose tissue. White adipocytes transform into beige adipocytes under the influence of external stimuli such as chronic exposure to cold, long-term therapy with PPAR-γ agonists (such as pioglitazone), or by two products of exercise: the hormone irisin and lactate (Sidossis & Kajimura, 2015).

**Regulation of energy balance, adiposity, and body weight**

The body's energy, adiposity, and weight are carefully held in balance by the interplay of numerous enzymes, neurotransmitters, hormones, and peptides, involving multiple coordinated regulatory circuits and feedback loops. Neural and hormonal mediators gauge fuel stores and energy expenditure, communicate cellular and systemic energy needs, and adjust metabolic processes to achieve a steady supply of energy to all cells.

**Adipose tissue regulation of energy balance**

Lipid exchange in adipocytes and other tissues is controlled by lipases, which are enzymes capable of breaking the bonds of triglycerides. In order for fatty acids to be taken up from the circulation, lipoprotein lipase (LPL) is secreted by adipocytes into the adipose capillaries, where it breaks down circulating triglycerides to glycerol and fatty acids. The fatty acids enter the adipocyte where they are recombined with other fatty acids and glycerol to reform triglycerides for storage in the lipid droplet (Lieberman & Lichtenberg, 2014). When fatty acids are needed for fuel, adipose triglyceride lipase (ATGL) performs the first step in the lysis of triglycerides to diglycerides in adipocytes, releasing the liberated fatty acids into the circulation (Langin et al., 2005). However, when the body has higher needs for energy generation from fatty acids, catecholamine-mediated stimulation of adipocytes activates hormone-sensitive lipase (HSL), which hydrolyzes diglycerides and triglycerides, augmenting the release of fatty acids back into the circulation (Langin et al., 2005). Individuals with obesity appear to have decreased catecholamine-mediated lipolysis and a reduction in HSL expression, which may underlie the development of their obesity (Langin et al., 2005).

Adipocytes also secrete the hormone leptin, a key regulator of two opposing neural pathways within the hypothalamus to maintain energy balance and regulate adiposity. The orexigenic pathway facilitates gaining weight and increasing fat mass by stimulating hunger and food-seeking behavior, and decreasing energy expenditure, especially via skeletal muscle activity. Conversely, the anorexigenic pathway promotes weight and adipose reduction by suppressing hunger and food-seeking behavior while increasing energy expenditure. The anorexigenic pathway increases energy expenditure by increasing SNS activation and increasing the basal metabolic rate. This pathway also raises spontaneous nonexercise activity thermogenesis (NEAT) via subconscious and semiautomatic movements, such as fidgeting, pacing, and changing posture. Table 1 summarizes the major orexigenic and anorexigenic peptides and neurotransmitters that contribute to energy balance and body weight.

**Orexigenic pathway regulation of energy balance**

Within the arcuate nucleus of the hypothalamus, neurons that coexpress neuropeptide Y (NPY) and agouti-related protein (AgRP) are key mediators of the orexigenic pathway (Figure 1). NPY and AgRP influence the increase in food consumption and decrease in energy expenditure (Frankish, Dryden, Hopkins, Wang, & Williams, 1995; Stephens et al., 1995). Secretion of NPY and AgRP is enhanced by fasting, uncontrolled diabetes, and leptin deficiency (Morton & Schwartz, 2001). NPY also functions in peripheral tissues, where it has hyperplastic effects on adipocytes, promotes adipogenesis, and blunts lipolysis (Zhang, Cline, & Gilbert, 2014). Ghrelin is an orexigenic signaling molecule secreted by the stomach. It is thought to initiate food consumption by activating NPY/AgRP neurons to secrete these two orexigenic neuropeptides (Nakazato et al., 2001).

Declining levels of ATP also activate the orexigenic pathway. When the ratio of adenosine monophosphate (AMP) to ATP rises, as in exercise, food deficits, and hypoxia, adenosine monophosphate kinase (AMPK) is activated to limit energy-consuming physiological processes (Hardie & Pan, 2002). In the hypothalamus, AMPK stimulates the release of NPY and AgRP to increase hunger and reduce energy expenditure (Hardie, Ross, & Hawley, 2012).

**Anorexigenic pathway regulation of energy balance**

Leptin is a key suppressor of the orexigenic pathway and stimulator of the anorexigenic pathway (Figure 2). It is secreted by adipose cells, and the amount of circulating leptin is correlated with fat mass; therefore, individuals with obesity have higher leptin levels than individuals without obesity. Leptin crosses the blood–brain barrier and decreases signaling from NPY and AgRP neurons,
Table 1  Chemical mediators of energy balance

<table>
<thead>
<tr>
<th>Molecular signal</th>
<th>Action</th>
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<tbody>
<tr>
<td><strong>Orexigenic mediators</strong></td>
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<tr>
<td>Neuropeptide Y (NPY) &amp; AgRP (agouti-related protein)</td>
<td>Stimulate food-seeking and reduce energy expenditure.</td>
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<td>Activated in states of negative energy balance.</td>
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<td></td>
<td>Inhibit proopiomelanocortin (POMC) neurons, and activate second order neurons producing orexin.</td>
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<td></td>
<td>Suppressed by leptin and insulin.</td>
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<td>NPY increases serum glucocorticoid.</td>
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<td></td>
<td>Stress stimulates NPY secretion.</td>
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<td>Ghrelin</td>
<td>Secreted by the stomach.</td>
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<td></td>
<td>Increased before meals and decreased after eating.</td>
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<td></td>
<td>Strongly simulates feeding.</td>
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<td></td>
<td>Levels are high in the genetic obesity disorder Prader–Willi syndrome, characterized by a chronic feeling of hunger and food seeking.</td>
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<td>Orexin A and B (hypocretin)</td>
<td>Stimulate appetite.</td>
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<td></td>
<td>Secreted by hypothalamic neurons in response to ghrelin and low glucose levels.</td>
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<td></td>
<td>Promote glucose uptake and storage as triglycerol in adipocytes (lipogenesis) and inhibit lipolysis.</td>
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<td></td>
<td>Leptin inhibits orexin secretion and effects.</td>
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<tr>
<td><strong>Anorexigenic mediators</strong></td>
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<tr>
<td>Amylin</td>
<td>Cosecreted with insulin from pancreas in response to food ingestion.</td>
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<td></td>
<td>Delays gastric emptying, inhibits glucagon release to suppress hepatic glucose production via glycogenolysis and gluconeogenesis, and inhibits food intake.</td>
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<td></td>
<td>Levels increase with obesity, and decline with weight loss.</td>
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<tr>
<td>Cholecystokinin (CCK)</td>
<td>Secreted by the gastrointestinal tract in response to the presence of nutrients, particularly fats.</td>
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<td></td>
<td>Reduces the effects of ghrelin via vagal projections to hypothalamic pathways, inducing satiety, and suppressing fuel intake.</td>
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<td>Short-term mediator of energy balance.</td>
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<td>Glucagon-like peptide 1 (GLP-1)</td>
<td>Food intake stimulates secretion by intestine.</td>
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<td></td>
<td>Promotes development of pancreatic beta cells</td>
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<td></td>
<td>Augments glucose-stimulated insulin secretion and inhibits glucagon secretion to lower blood glucose levels.</td>
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<td></td>
<td>Delays gastric emptying.</td>
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<td></td>
<td>Reduces food ingestion through unknown mechanism.</td>
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<tr>
<td>Glucose</td>
<td>Only source of energy for neurons.</td>
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<td></td>
<td>Decreases hunger and food seeking.</td>
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<td></td>
<td>Dynamic decline in glucose utilization induces hunger and feeding behavior and promotes weight gain.</td>
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<tr>
<td>Insulin</td>
<td>Secreted by the pancreas. Inhibits hypothalamic NPY/AGRP neurons, and stimulates POMC neurons. Results in satiety and decreases feeding.</td>
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<td>Promotes energy expenditure.</td>
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<td>Promotes glucose uptake by muscles for energy expenditure, and facilitates depositing lipids in adipose tissue.</td>
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<tr>
<td>Leptin</td>
<td>Synthesized by adipose tissue.</td>
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<td></td>
<td>Reduces NPY and AgARP secretion and stimulates the POMC neurons to secrete the melanocortin, α-MSH, leading to reduced food consumption and increased energy output.</td>
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<td>Eight rare mutations, resulting in the absence of leptin, cause impaired satiety, intense hyperphagia, and the early development of obesity (Funcke et al., 2014).</td>
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<td>Recombinant human leptin can result in weight loss and restoration of endocrine and immune function in leptin-deficient individuals (Paz-Filho, Mastronardi, &amp; Licinio, 2015).</td>
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<td>Congenital deficiency in the leptin receptor, results in a similar phenotype to leptin-deficiency, which cannot be rectified with recombinant human leptin (Farooqi et al., 2007).</td>
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<tr>
<td>Melanocortins (α-melanocyte stimulating hormone; α-MSH, β-MSH)</td>
<td>Produced by POMC neurons in the hypothalamus. Stimulates melanocortin 4 receptor (MC4R) on second order neurons to decrease feeding and increase energy expenditure.</td>
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<td>By interfering with the transmission of anorexigenic signals, MC4R mutations and autoantibodies block signals to decrease food consumption and increase energy expenditure.</td>
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<td>MC4R mutations are the leading cause of monogenic obesity, and occur in 5%–6% of people with obesity (Farooqi &amp; O’Rahilly, 2008; Reinehr et al., 2009). Some individuals with obesity have MC4R autoantibodies in their serum (Peter et al., 2009).</td>
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<tr>
<td>Molecular signal</td>
<td>Action</td>
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<tr>
<td><strong>Anorexigenic mediators</strong></td>
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<tr>
<td>Peptide YY (PYY)</td>
<td>Secreted by ileum and colon after feeding.</td>
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<tr>
<td></td>
<td>Inhibits NPY and AgRP.</td>
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<tr>
<td></td>
<td>Reduces appetite.</td>
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<tr>
<td>Thyroid hormone</td>
<td>T₃ stimulates metabolic activity in most body tissues.</td>
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<tr>
<td>(tri-iodothyronine, T₃;</td>
<td>Enhances adenosine triphosphate (ATP) production in cells systemically and generates heat.</td>
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<tr>
<td>thyroxine, T₄)</td>
<td>T₃ stimulates carbohydrate utilization and supports lipolysis.</td>
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<tr>
<td></td>
<td>Promotes fatty acid oxidation.</td>
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<tr>
<td><strong>Mixed-effect mediators</strong></td>
<td></td>
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<tr>
<td>Serotonin</td>
<td>Produced centrally in the central nervous system (CNS) and peripherally in the gastrointestinal (GI) tract. Centrally, serotonin decreases appetite and promotes weight loss. Peripheral serotonin increases lipogenesis in white adipocytes and promotes weight gain. Several single nucleotide polymorphisms genes coding for serotonin receptors are associated with obesity and metabolic syndrome (Oh, Park, &amp; Kim, 2016).</td>
</tr>
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Reducing their hunger and feeding signals. Leptin simultaneously activates the anorexigenic pathway by stimulating pro-opiomelanocortin (POMC) neurons, which in turn release alpha- and beta-melanocyte stimulating hormones (α- and β-MSH; Bertagna, 1994). Melanocyte-stimulating hormones promote satiety, diminish food intake, and elevate energy expenditure.

Leptin also increases SNS signaling that increases skeletal muscle tone, facilitates glucose and fatty acid oxidation, and increases brown-fat thermogenesis, resulting in...

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**Figure 1** Orexigenic signaling. When fuel substrates are low or energy expenditure is high, a negative energy balance stimulates orexigenic signaling (solid arrows). Lower glucose, insulin, leptin, and higher adenosine monophosphate kinase (AMPK) will provoke the release of neuropeptide Y (NPY) and agouti-related protein (AgRP) to increase feeding and conserve energy; these adaptations will also inhibit signals of satiety and energy expenditure permissiveness from proopiomelanocortin (POMC) neurons.
Figure 2 Anorexigenic signaling. Food consumption leads to increased anorexigenic signaling (solid arrows). Rising glucose, insulin, and amylin activate proopiomelanocortin (POMC) and cocaine-amphetamine regulator transcriptase (CART) peptide neurons in the hypothalamus. Alpha melanocyte stimulating hormone-3 (α-MSH3) secretion increases so that feeding subsides, and there is an increase in spontaneous activity. Storage of fatty acids as lipid stimulates increased release of leptin from adipose tissue and increases anorexigenic signaling from the POMC/CART neurons. At the same time, the orexigenic signals from neuropeptide Y (NPY)/agouti-related protein (AgRP) neurons are inhibited, reducing hunger and energy conservation signals.

Glucose is another source of anorexigenic signaling. As the primary source of energy for neurons (Chih & Roberts, 2003), glucose is a short-term signal of the availability of adequate fuel (Routh, Hao, Santiago, Sheng, & Zhou, 2014). Rising blood glucose decreases hunger and food intake (Mayer, 1955). It is believed that glucose receptor neurons in the hypothalamus detect tissue utilization of glucose, independent of absolute blood glucose levels, prompting food-seeking behavior. Conversely, the detection of increased glucose utilization results in decreased hunger and cessation of feeding. There is evidence that lower blood glucose, or reactive hypoglycemia, at the end of the weight-loss program appears to be a strong predictor of weight regain when followed up 6 years later (Boule et al., 2008).

Insulin secretion reinforces glucose’s anorexigenic message by decreasing NPY/AgRP expression (Kalra et al., 1999). Insulin also promotes leptin secretion from adipocytes along with an increase in melanocortin expression (Plum, Belgardt, & Bruning, 2006), bolstering signals to decrease feeding and increase energy expenditure.

Like leptin, thyroid hormone intersects the orexigenic and anorexigenic pathways to control energy balance, adiposity, and body weight. Two forms of thyroid hormone, the prohormone thyroxine (T₄) and triiodothyronine (T₃) are secreted by the thyroid gland under the influence of thyroid-stimulating hormone (TSH). T₃ increases metabolic activity in virtually all body tissues and plays a role in weight regulation. In addition, T₃ stimulates carbohydrate uptake and metabolism and promotes lipolysis and oxidation of fatty acids for energy (Hall, 2016). One of the ways leptin increases energy expenditure is by raising T₃ to increase the metabolic rate.

Cholecystokinin (CCK; Little, Horowitz, & Feinle-Bisset, 2005), amylin (Roth, Erickson, Chen, & Parkes, 2012),
glucagon-like peptide 1 (GLP-1; Hayes, Mietlicki-Baase, Kanoski, & De Jonghe, 2014; Müller, Heppner, Yi, Pflugger, & Matthias, 2014), and peptide YY (PYY; Lean & Malkova, 2016) are other anorexigenic mediators of energy balance. GLP-1, CCK, and PYY are involved as part of the gut–brain axis in the homeostasis of body weight (Table 1; Lean & Malkova, 2016). The incretin, GLP-1, is secreted in response to fat and carbohydrate intake and promotes glucose homeostasis by inducing insulin release and inhibiting glucagon secretion (Table 1; Lean & Malkova, 2016). GLP-1 slows the rate of gastric emptying (Roth et al., 2012) and regulates food intake and appetite. While the mechanism of action for the effect on food intake and appetite are not fully understood, it may involve stimulation of the POMC/cocaine-amphetamine regulator transcriptase (CART) neurons and indirect inhibition of neurons expressing NPY and agouti-related peptide AgRP in the hypothalamus (Secher et al., 2014). One GLP-1 receptor agonist, liraglutide, has been U.S. Food and Drug Administration (FDA) approved for use in management of T2D at a maximum dose of 1.8 mg (Victoza®; Novo Nordisk). GLP-1 receptor agonists provide for treatment of T2D include exenatide (Byetta®; AstraZeneca, London, UK), dulaglutide (Trulicity®; Eli Lilly & Co., Indianapolis, IN, USA), and albiglutide (Tanzeum®; GlaxoSmithKline, London, UK). CCK and PYY also provide a link between gut and brain as they are released by the gut in response to food and act either via the afferent nerves, or directly in the brain, to inhibit NPY/AgRP neurons (Konturek, Konturek, Pawlik, & Brzozowski, 2004; Little et al., 2005). Given the close links between the gut and the brain, it is unsurprising that the composition of gut microbiota may impact the regulation of energy balance and the development of obesity, both in terms of direct effect on digestion and metabolism but potentially by affecting the regulation of the gut–brain axis and other mechanisms (Moreno-Indias, Cardona, Tinahones, & Queipo-Ortuno, 2014).

Extrahypothalamic energy mediators

In addition to signaling molecules influencing energy regulation via the hypothalamus, other mediators influence energy balance in tissues outside the hypothalamus. Serotonin is a neurotransmitter involved in a range of functions including sleep, pain sensitivity, blood pressure, and mood (Wurtman & Wurtman, 1995). Serotonin exerts influence over energy homeostasis through both hypothalamic pathways and peripheral pathways. Within the hypothalamus, serotonin activates POMC neurons and inhibits NPY/AgRP neurons to reduce feeding behavior. Despite centrally acting serotonin having anorexigenic effects, serotonin is linked with carbohydrate craving as carbohydrate, but not protein, consumption leads to serotonin production in the brain (Wurtman & Wurtman, 1995). Hence, some individuals crave carbohydrate as a way to improve their mood via the stimulation of serotonin secretion.

Serotonin reuptake inhibitors, including sertraline (Zoloft®; Pfizer, New York, NY, USA) and fluoxetine (Prozac®; Eli Lilly & Co.) reduce food intake and promote weight loss in some patients by increasing central serotonin concentrations (Namkung, Kim, & Park, 2015). Some currently prescribed weight loss medications target central serotonin levels. Lorcaserin hydrochloride (HCl; Belviq®; Eisai Co., Tokyo, Japan) specifically activates serotonin 2C receptors. The phentermine component of the phentermine/topiramate medication combination (Qsymia®; Vivus, Inc., Mountain View, CA, USA) stimulates synaptic noradrenaline, dopamine, and serotonin release (Manning, Pucci, & Finer, 2014). These drugs may be useful in individuals with carbohydrate craving.

Despite short-term weight loss following initiation of SSRI therapy, weight gain is common in patients taking these agents for 3 months or longer (Himmerich, Schuld, Haack, Kaufmann, & Pollmacher, 2004), and is an expected outcome of these medications. Although initially acting as anorexigenic agents, SSRIs are thought to cause weight gain by downregulating available serotonin receptors, and increasing food intake (Schwartz, Meszaros, Khan, & Nihalani, 2007). Moreover, peripheral serotonin blunts the effects of beta-adrenergic signaling in brown and beige adipocytes, reducing energy expenditure by these fat cells. It also increases lipid storage in white adipocytes, and promotes adipocyte differentiation by activating PPAR-γ (Watanabe, Rose, & Aso, 2011). As a result, peripheral serotonin facilitates lipid storage and suppresses energy expenditure over time.

Leptin and glucose also influence energy regulation via neural circuits outside the hypothalamus. In the midbrain, leptin and glucose stimulate the release of dopamine. Dopamine is a neurotransmitter involved in mood, motivation, adaptive learning, perception of exertion, estimation of effort-related costs, and behavior activation (Salamone & Correa, 2012). Binding of dopamine to dopamine 2 receptors (D2Rs) on mesolimbic neurons is necessary to attain the anorexigenic effects of leptin, and to inhibit normal dietary ingestion after fasting (Billes, Simonds, & Cowley, 2012). The leptin–D2R anorexigenic effects are independent of melanocortin and ghrelin signaling via the hypothalamus. The anorexigenic effects are also independent of taste, and depend on foods’ caloric load rather than palatability (de Araujo et al., 2008).
The reduction in feeding following ingestion of calorie-dense foods indicates that dopamine signaling may serve as a central calorie sensor that regulates food intake and energy balance according to the caloric density of a meal.

Genetic polymorphisms of genes affecting dopamine function have been linked to the increased risk for obesity, and hypodopaminergic function has a central role in reward deficiency syndrome (RDS), which results in abnormal craving behavior (Blum, Thanos, & Gold, 2014). Binge eating promotes the production and utilization of dopamine in the brain (Blum et al., 2014), so for some individuals, and perhaps particularly for those who have poor dopamine responses to other stimuli, binge eating can become a way to improve their mood and motivation through a dopamine-mediated pathway. Because the bupropion component of naltrexone/bupropion (Contrave®; Orexigen Therapeutics, Inc., La Jolla, CA, USA) is a weak inhibitor of the neuronal reuptake of dopamine and norepinephrine (Stahl et al., 2004), its use in individuals with food-binging behavior may need to be considered carefully given the links between the hypodopamine and binge eating described by Blum et al. (2014).

**Physiological effects of weight loss and weight regain**

When individuals lose weight through calorie restriction (with or without pharmacologic intervention), increased physical activity, or bariatric surgery, they activate physiological processes to regain the lost weight and adipose tissue mass. This is thought to be a biological compensatory mechanism aimed at preventing excessive weight loss and the development of a severe catabolic state (Figure 3; MacLean, Higgins, Giles, Sherk, & Jackman, 2015).

**Neuroendocrine signaling adaptation**

Weight loss necessarily results from a negative energy balance, in which energy expenditure exceeds fuel intake. As fat mass declines, leptin secretion is diminished. Lower leptin levels permit increased NPY/AgRP nerve transmission and silence the anorexigenic leptin–melanocortin
pathway. With food restriction and weight loss, glucose, insulin, leptin, and melanocyte-stimulating hormones are reduced, and NPY and AgRP signaling increase. Likewise, when individuals with obesity increase their energy expenditure through physical exercise, they decrease glucose and insulin concentrations and increase AMPK production. Lower glucose, insulin, and higher AMPK will provoke the release of NPY and AgRP to increase feeding and conserve energy; these adaptations will also inhibit signals of satiety and energy expenditure permissiveness from POMC neurons.

In response to the alterations in neuroendocrine signals associated with weight loss, systemic metabolic changes facilitate weight regain. Following weight loss, an individual will experience an approximately 15% reduction in 24-h energy expenditure, accomplished by lowering SNS tone and strengthening parasympathetic system activity. In addition, T3 secretion declines (Rosenbaum, Leibel, & Hirsch, 1997), but may not appear as overt clinical hypothyroidism. Both the reduction in SNS innervation and T3 synergistically lower oxygen consumption, basal metabolic rate, and skeletal muscle tone (Donangelo, 2014; McAninch & Bianco, 2014). The net effect of decreased thyroid function supports the overall reduction in resting energy expenditure and 24-h total energy expenditure (Rosenbaum, Hirsch, Murphy, & Leibel, 2000).

In response to weight loss, there is a decline in fatty acid to ATP conversion. A weight reduction of approximately 10 kg (22 lb) results in diminished fat oxidation by 20 g, or ~180 calories/day (Schutz, Tremblay, Weinsier, & Nelson, 1992). Lowering fat oxidation limits the ability to engage in sustained intentional activity, therefore making it harder to expend energy to continue weight loss.

The involuntary reduction in 24-h energy expenditure cannot be overemphasized. In order to maintain the weight loss, a person with obesity who loses weight must consume 15% fewer calories than a person of the same age and sex who has never been affected by obesity (Rosenbaum & Leibel, 1998). Alterations in hypothalamic energy signaling and the decreased energy expenditure have been shown to persist for years, or until the weight is regained (Rosenbaum et al., 1997; Sumithran et al., 2011). These involuntary physiologic adaptations to weight loss oppose the conscious, voluntary methods employed by individuals to control their obesity through diet and exercise. Biologic compensation for weight loss is achieved by altering energy expenditure, mostly achieved by changes in the amount of energy spent in NEAT (25%), rather than through changes in resting energy expenditure (18%; Rosenbaum & Leibel, 1998). As predicted by set-point theory, individuals with obesity defend a higher body weight or fat mass than those who have never had obesity; the reason for this defense of a greater fat mass is unknown.

Skeletal muscle performance

Skeletal muscle performance adapts in response to negative energy balance to resist body weight, adipose tissue, and muscle loss. During maintenance of a 10% body-weight reduction, adults demonstrate increased skeletal muscle efficiency, thus requiring fewer calories per unit of work than before the weight loss (Goldsmith et al., 2010; Rosenbaum et al., 2003). This increased muscle efficiency accounts for approximately 35% of the change in nonresting daily energy expenditure (Rosenbaum et al., 2003). Surprisingly, low-level physical activity intensity has a more profound effect on increasing skeletal muscle efficiency than does a high-intensity exercise workload. Therefore, calories expended by adding 30–60 min of moderate- or high-intensity daily physical activity in hopes of facilitating weight loss are offset by involuntarily increased muscle efficiency during low-level routine activity for the remainder of the day. The increased energy efficiency will promote weight regain and recovery of fat mass. Despite the impact of increased muscle efficiency, increasing physical activity can improve blood pressure, lipid profile, and systemic inflammation associated with obesity (Murdy & Ehrman, 2013). Additionally, exercise can also assist in dissipating energy by increasing beige adipocytes through the actions of irisin and lactate.

During weight loss, both fat and lean (muscle) tissue are lost, although loss of fat mass is greater than muscle losses. It has been found that those who regain more than 2 kg of weight trend toward a greater accumulation of fat mass than lean tissue (Beavers et al., 2011).

Adipose tissue

The buildup of fat mass disproportionately faster than lean or muscle tissue with refeeding following food restriction has been termed “catch-up fat.” Catch-up fat has been found to occur even when the person is eating a diet with adequate protein intake. It has been observed in low-birthweight infants, and children and adults subjected to undernutrition or malnutrition because of famine, wars, chronic illness, voluntary calorie restriction, and weight regain following bariatric surgery (Dulloo, Jacquet, & Montani, 2002). The accumulation of fat faster than lean tissue is accelerated with a high-fat diet, but can occur on a low-fat diet. Fat-mass recovery is facilitated in part by the alterations in adipose and muscle utilization of glucose. Insulin-stimulated glucose utilization increases in adipose tissue and is reduced in muscle tissue.
(Cettour-Rose et al., 2005). The replenishment of fat stores may also result from decreased SNS inhibition of adipogenesis during weight loss (Bartness et al., 2014), giving rise to small new adipocytes primed to store lipids when they become available. Thus, undernutrition may be an important and largely unrecognized forerunner of excess weight gain and obesity in children and adults. Catch-up fat is also associated with reduced blood flow to muscles and increased cardiometabolic risk (Beavers et al., 2011; Cettour-Rose et al., 2005; Dulloo et al., 2002).

**Clinical practice implications of weight regain following successful weight loss**

Since the time of Hippocrates, treatment of obesity has centered on the need for the obese person to eat less and exercise more (Stunkard, 1958). These modalities remain the cornerstones of current recommendations for the management of obesity by the American Nurse Practitioner Foundation (ANPF, 2013), the American Heart Association (AHA, 2014), the American College of Cardiology (ACC), and The Obesity Society (TOS; Jensen et al., 2014). Mounting scientific evidence undercuts the utility of this paradigm of obesity by showing that the body’s energy balance, weight, and adiposity are intricately controlled by biological processes resistant to voluntary manipulation, such as those advocated in clinical guidelines. Clinical investigations have shown the benefit of short-term weight loss for improving dyslipidemia, blood glucose, and blood pressure. They also clearly and consistently show that lifestyle, pharmacologic, and surgical weight-loss interventions evoke powerful and persistent physiological responses to regain the lost weight. Research also shows that repeated attempts to lose weight do not abolish the physiological adaptation that leads to weight regain; nor do they correct any underlying genetic or environmental disruptions in the processes of converting fuel to energy and maintaining energy balance. The biological pressures to increase feeding and decrease energy expenditure “do not resolve with time after weight loss; rather they may even strengthen with time during weight loss maintenance” (MacLean, Blundell, Mennella, & Batterham, 2017, pp. S12–S13). Changes in neuroendocrine signaling, skeletal muscle efficiency, and adipogenic mediators drive weight regain for most patients, and often have deleterious effects on the metabolic profile the weight loss efforts are intended to improve.

For clinicians and patients battling the problem of obesity, understanding the biology underlying the development of obesity and weight regain following weight loss can be daunting and discouraging, because it runs counter to our socially instilled beliefs about obesity. Furthermore, the science refuting the long-term effectiveness of a negative energy balance to achieve weight loss does not offer an immediate solution to the problem of obesity, and, therefore, may seem clinically irrelevant. It would be easy for many clinicians to draw the wrong conclusion, that there is nothing we can do to change clinical practice and improve care. However, we can find a model for changing our care of obese patients in the work of Kübler-Ross (1969) in revolutionizing the care of terminally ill patients. As she demonstrated, curing terminal illness was not required to make a profound difference in the care of dying patients. Similarly, although desirable, it is not essential to find the treatment that will provide permanent weight loss to improve the care of obese patients. What we need is a change in our approach to a problem we cannot make go away with our current level of science.

Just as Kübler-Ross opened the door to forthright discussions with patients about death and dying, nurse practitioners can take a leadership role in educating patients about the biology of obesity and weight regain. When presenting weight-loss strategies, we can respect their dignity and autonomy by acknowledging the existence of adaptive biological processes. We must present realistic expectations with regard to weight-loss goals and the likelihood of weight regain despite patient motivation and intention. Providing a general biological rationale for weight regain will help to inform patients and help allay the frustration of “failure.” These discussions are needed to provide frank recognition of the obstacles people with obesity will face each day in their valiant efforts to fight a lifelong-disease process. It should be as professionally unacceptable to withhold information about the biology of obesity and weight regain from an obese person as it is to withhold a terminally ill patient’s diagnosis and prognosis.

It is imperative for nurse practitioners to put aside the notion that obesity is a problem of too much intake and too little exercise. They must look beyond diet and exercise for the etiology and management of obesity, and confront nontraditional ideas about factors contributing to the development of obesity. As the ANPF noted, numerous “noncaloric” factors contribute to the development of obesity, such as obesogenic medications (ANPF, 2013; Cheskin et al., 1999; Leslie, Hankey, & Lean, 2007; Ratliff, Barber, Palmese, Reutenauer, & Tek, 2010), sleep deficiency (Ruan, Xun, Cai, He, & Tang, 2015; Wu, Zhai, & Zhang, 2014), and alterations to the gastrointestinal microbiome (Musso, Gambino, & Cassader, 2010). Aggressively assessing and managing these underlying contributors to obesity is vital to clinical management of this disease.

Teaching patients about biological adaptation to weight loss paves the way for discussing the obese patient’s experiences while also bringing out their associated physical, psychological, and social needs. As discussed in
this supplement (Ritten, 2017), we can address obese patients’ need for personal dignity by confronting weight bias and making use of appropriately sized furnishings and medical equipment. We can advise lifestyle changes such as physical activity and improved sleep patterns, which can provide health benefits independent of weight loss.

When patients do choose to engage in a weight-loss regimen, it is essential to closely monitor changing body composition. Tracking changes in body weight and BMI is standard practice, but these parameters are insufficient for gauging the metabolic effects of weight loss. Because both fat and lean tissue will be lost as a result of calorie restriction, and both resting and 24-h energy expenditure will decline, it is necessary to regularly assess muscle mass and estimated basal metabolic rate (BMR). Technology has advanced to make bioimpedance body composition analyzers or scales economically feasible for home use, as well as clinical settings. While these devices may not be suitable for use with patients who have pacemakers or implantable cardioverter defibrillators (Buch, Bradfield, Larson, & Horwich, 2012), they provide an economical way of tracking how weight loss is affecting muscle adaptation and energy expenditure. Many of these devices are able to upload body composition information to a smartphone or computer so that trends can be tracked over time. Weighing on these scales once a week can provide the earliest evidence of a downward trend in muscle mass and BMR. Early recognition of these indicators that the body’s adaptive mechanisms have been stimulated to protect the body’s energy balance may enable us to begin developing and testing targeted strategies to stabilize energy expenditure and sustain weight loss.

Genomic testing needs to be explored with patients. Most obese patients are not offered genomic testing, even though obesity is highly heritable, because there is no current treatment or cure except in rare disorders like leptin deficiency (Ng & Bowden, 2013). As we have shown, multiple genetic variants can disrupt energy balance via multiple pathways, making obesity a heterogenous disease. The time has come to assess and study what distinguishes different types of obesity clinically, and to investigate what works for subgroups of patients with different genetic predispositions. For example, it is unlikely that the same interventions will be equally successful in managing obesity resulting from melanocortin receptor mutations, FTO gene variants, and beta adrenergic receptor polymorphisms. Genomic testing can also offer many obese patients an explanation for their obesity. Just as it matters to patients what kind of cancer they have, it matters to obese patients why they are obese.

Finally, nurse educators must tackle the need for nurses to have greater understanding of the biology of obesity and weight regain. Undergraduate and graduate nursing curricula need to include content on the pathophysiology of obesity and weight regain alongside obesity management guidelines. Professional organizations need to present more opportunities for continuing education offerings related to the pathophysiology of obesity and weight regain to assist clinicians to incrementally expand their understanding of this complex problem. More research is needed to discover best practices for addressing the problems associated with weight regain, especially patients’ psychosocial responses to repeated treatment “failures.”

Conclusion

Traditionally, obesity research and practice has focused on inducing a negative energy balance. We are entering an era when obesity management must shift to focus on the problems of physiological adaptation to negative energy balance and weight regain to improve the health of people with obesity.

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References

Biology of obesity and weight regain


~M. M. Rogge & B. Gautam~

**Biography of obesity and weight regain**

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